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Congenital Diaphragmatic Hernia:
Updates and Outcomes

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Drs Benjamin, Bizzarro, and Cotton have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Abstract
Management of congenital diaphragmatic hernia (CDH) remains challenging. Despite advances in technologic and therapeutic strategies such as high-frequency mechanical ventilation, inhaled nitric oxide (iNO), and delayed surgical repair, the condition continues to carry a substantial mortality risk. In recent years, with increasing prenatal identification of fetuses affected by CDH, more effort has been directed toward strategies allowing in utero intervention, with the goal of improving survival. Unfortunately, a universally successful fetal treatment for CDH remains elusive. Over the past several decades, collective knowledge has markedly increased regarding the range of short- and long-term morbidities experienced by CDH survivors, and medical care has evolved as understanding of the disease has progressed. Affected patients demand and deserve a multidisciplinary approach, both in the inpatient arena and follow-up setting, with experts in neonatology, surgery, pulmonology, cardiology, and neurodevelopment working together to optimize outcomes. This article reviews the basic pathophysiology behind CDH, describes recent updates in the field, and outlines the long-term outcomes for these fascinating and complex patients.

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

1. Define the cause, incidence, and pathophysiology of CDH.
2. Discuss the results from recent studies of fetal surgical intervention for CDH.
3. Discuss the primary cardiorespiratory management principles for the infant who has CDH.
4. Explain why, and to what extent, infants who have CDH are at risk for continued pulmonary, gastrointestinal, and neurodevelopmental complications throughout childhood.

Abbreviations

CDH:	congenital diaphragmatic hernia
cGMP:	cyclic guanosine 5'-monophosphate
ECMO:	extracorporeal membrane oxygenation
GER:	gastroesophageal reflux
iNO:	inhaled nitric oxide
MRI:	magnetic resonance imaging
NICU:	neonatal intensive care unit
PPHN:	persistent pulmonary hypertension of the newborn
TO:	tracheal occlusion

Introduction and Background

Infants who have CDH are among the most medically challenging patients in the neonatal intensive care unit (NICU). Although the pathophysiology of the condition is relatively straightforward (abnormal development of the diaphragm allows herniation of abdominal contents into the chest cavity, thereby inhibiting and altering lung development), clinical care is arduous and complex. CDH is associated with a substantial mortality risk, and those who survive the newborn period often encounter struggles in the months and years ahead. Nevertheless, CDH survivors provide a unique sense of satisfaction and joy to those who care for them; despite the difficulties, the potential for lasting health and well-being is great.

CDH occurs because of a developmental defect in the formation of the diaphragm between weeks 8 and 10 of gestation. The diaphragmatic defect allows abdominal organs (intestines, stomach, liver, and spleen) to herniate into the chest cavity at a critical stage of embryogenesis, during the time of bronchial and pulmonary artery branching. With abdominal contents in the chest cavity,

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lung growth and development are impaired, resulting in pulmonary parenchymal and vascular hypoplasia. Although lung hypoplasia is most significant on the side of the diaphragmatic defect, both lungs may be affected.

The hypoplastic lungs in CDH contain fewer airways, vessels, and alveolar structures. In addition, the pulmonary vasculature is markedly abnormal, consisting of hypermuscular peripheral pulmonary arteries. Such alterations in anatomy may have enormous physiologic consequences. Fixed increased vascular resistance and decreased surface area for gas exchange (1) may translate clinically into persistent pulmonary hypertension of the newborn (PPHN) and inadequate oxygenation of vital tissues and organs. Hypoxemia and metabolic acidosis promote further pulmonary vasospasm, stimulating a vicious cycle that leads to rapid clinical deterioration.

Many CDH survivors have long-lasting respiratory issues, including chronic lung disease, bronchial hyperreactivity, and pulmonary hypertension. (2)(3) However, the difficulties CDH survivors experience extend beyond the respiratory system. Most are diagnosed with symptomatic gastroesophageal reflux (GER) as a consequence of the abnormal location of the stomach and intestines during fetal development. CDH survivors are at increased risk for growth and nutrition difficulties, including feeding problems and failure to thrive. (4)(5)(6) In addition, a significant number show evidence of neurocognitive delay, hearing impairment, and behavioral disorders (7)(8)(9)(10) in childhood and adolescence.

Epidemiology and Anatomy

CDH is estimated to occur in 1 of every 3,000 live births. (11) The true incidence remains unknown because of early deaths among severely affected fetuses and infants, (12) which is commonly described as the "hidden mortality" of CDH. Most population studies have not found a sex association in CDH.

Three CDH subtypes are described, depending on the location of the diaphragmatic defect: the most common Bochdalek type, resulting from a posterolateral defect; the Morgagni type, resulting from an anterior defect; and the pars sternalis type, which occurs due to a central diaphragmatic defect. Eighty-five percent of diaphragmatic defects occur on the left side, 13% are right-sided, and 2% are bilateral. Right-sided defects are associated with a higher mortality (45% to 80%) because of the presence of the liver in the chest. (13) Bilateral absence of the diaphragm is a rare and universally fatal condition.

In approximately 50% to 60% of cases, CDH occurs as an isolated finding. "Complex" or "syndromic" CDH describes the remaining cases, in which CDH is coupled with chromosomal abnormalities or other major malformations. The most commonly associated developmental anomalies affect the cardiac (60%), renal (23%), gastrointestinal (17%), and nervous systems (14%). (14) CDH may be associated with single gene disorders or chromosomal aberrations, as in Turner syndrome, trisomy 13, and trisomy 18. CDH also occurs as a prominent feature of Fryns syndrome, which includes a diaphragmatic defect as one of the primary diagnostic criteria. Reports have linked right-sided CDH with group B streptococcal infection. In isolated CDH, the primary determinants of survival are the degree of pulmonary hypoplasia and severity of pulmonary hypertension. The presence of additional anomalies or chromosomal aberrations is associated with decreased survival. (15) Early prenatal diagnosis, (16) prematurity, (17) low birthweight, (18) and pneumothorax (19) are other factors that have been associated with poor outcome.

In the past decade, significant technological and medical advancements have enhanced the care of critically ill infants. Despite these improvements, survival for infants who have CDH has remained static, primarily due to the number of deaths occurring outside tertiary care centers. Over the past several years, certain high-volume centers have reported survival rates approaching 90% or more, (20)(21)(22) which may be explained partly by case selection bias. Nevertheless, overall survival for isolated CDH remains between 50% and 80%. (12)(23)

Antenatal Diagnosis and Management

Using ultrasonography, the gold-standard technique for antenatal diagnosis of CDH, most cases are identified prenatally, (24) often between 16 and 24 weeks of gestation. The characteristic ultrasonographic finding of left-sided CDH is detection of the fluid-filled stomach within the lower thorax. Right-sided CDH is more difficult to diagnose antenatally because the herniated viscera consists predominantly of the right lobe of the liver, which has a similar echogenicity to the fetal lung. Doppler examination of the umbilical vein and hepatic vessels can be useful in this situation. Additional findings such as polyhydramnios, small abdominal circumference, and mediastinal or cardiac shift away from the side of the hernia may suggest a fetus that has CDH. Other diagnoses that should be considered include congenital cystic adenomatoid malformation, bronchopulmonary sequestration, and diaphragmatic eventration.

Once a CDH is discovered, further testing is warranted to determine whether the diaphragmatic defect is

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an isolated finding or associated with other anomalies. More detailed anatomic ultrasonography should be performed as well as amniocentesis to detect chromosomal disorders. Determination of liver position (above or below the diaphragm) and an estimation of lung-to-head ratio (measurement of the contralateral lung in comparison with head circumference to correct for gestational age, which provides an indirect assessment of the degree of pulmonary hypoplasia) may be useful in predicting outcome. (25) Fetal magnetic resonance imaging (MRI) is being used more commonly to delineate the extent of liver herniation. Better understanding of disease severity allows more appropriate parental counseling (including the option of pregnancy termination in certain cases), more accurate assessment regarding prognosis, and determination of eligibility for fetal surgical intervention. Antenatal counseling also often includes recommendations for delivery at a tertiary care center, where the timing of delivery can be optimized and coordinated with experienced specialists in neonatology, cardiology, and pediatric surgery. Currently, the standard antenatal approach to a fetus with CDH remains expectant management, with close and frequent monitoring for the development of complications. Ideally, labor is induced around 38 weeks' gestation to allow controlled delivery in a tertiary care center that can offer all advanced strategies for respiratory failure, including extracorporeal membrane oxygenation (ECMO).

Fetal Surgery

A successful fetal therapy could be the answer to the problem of CDH. Theoretically, promoting fetal lung growth would increase the likelihood of postnatal survival. Early experiments in large animals demonstrated that in utero repair of the diaphragmatic defect could be achieved, (26) but the procedure proved technically impossible in humans due to kinking of the umbilical vein as the liver was displaced from the chest. (27) More recent studies have investigated the strategy of temporary tracheal occlusion (TO) to induce fetal lung growth. During gestation, the fetal lung actively secretes fluid into the airways, which is drained to the amniotic cavity during fetal breathing movements. (28) By occluding the fetal trachea with a balloon, lung growth is stimulated as the retained fetal lung fluid provides gentle distention of lung tissue. (29) TO has been shown to reverse pulmonary hypoplasia in animal models of CDH. (30) However, despite sound theoretical science and demonstrated success in animal models, none of the trials in humans has demonstrated significant benefit for prenatal surgical intervention compared with standard postnatal therapy, primarily because of the increased rates of preterm delivery following fetal intervention (Table 1). Although studies have yielded disappointing results to date, new clinical trials continue in the United States and internationally as researchers work toward an in utero cure for CDH (clinicaltrials.gov, NCT00763737, NCT00373438).

Postnatal Management

Initial Resuscitation and Stabilization

A recent consensus statement from the CDH EURO Consortium describes a standardized protocol for treatment of the infant who has CDH. (36) Because no similar consensus statement has been drafted in the United States, substantial center-to-center variability exists regarding specific management strategies for CDH. The following discussion of detailed management practices for infants who have CDH is not necessarily universally accepted. Most centers agree on the delivery room approach to the infant in whom CDH is prenatally diagnosed.

Infants who have symptomatic CDH usually present with respiratory distress and cyanosis in the first few minutes to hours after birth. Physical examination may demonstrate a scaphoid abdomen, barrel-shaped chest, and increased work of breathing (retractions, grunting, tachypnea). Auscultation reveals decreased aeration over the ipsilateral chest, with heart tones shifted to the contralateral side. Bowel sounds may be appreciated in the chest, and chest radiography typically shows multiple gas-filled bowel loops within the thorax (Figure). Following delivery, swallowed air leads to intestinal distention that worsens lung compression and mediastinal shift, causing increasing respiratory distress. If mediastinal compression is severe, venous return may be impaired, leading to hypoperfusion and systemic hypotension. The resultant acidosis and hypoxemia further exacerbate the cycle of pulmonary vasoconstriction and hypoxemia.

A prenatal diagnosis of CDH indicates the need for immediate postnatal endotracheal intubation and mechanical ventilation to avoid the risk of intestinal distension. Bag-valve-mask ventilation should be avoided. An adequate-sized nasogastric tube should be placed and connected to continuous suction to allow intestinal decompression. In the NICU, continuous pre- and postductal pulse oximetry is used to assess the degree of PPHN via right-to-left shunting at the level of the ductus arteriosus. Placement of umbilical arterial and venous catheters allows for continual blood pressure monitoring, blood gas sampling, fluid administration, and ino-

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Table 1. Summary of Fetal Surgical Trials for Congenital Diaphragmatic Hernia

Author, Year, Study Design	Methods	Inclusion Criteria	Survival	Other Findings	Conclusion(s)
Harrison, et al (31), 1997 Prospective	Open fetal surgery (n=4) versus standard postnatal care (n=7)	CDH, no liver herniation	Open 75% versus standard 86%	Fetal surgery group born more prematurely (32 wk versus 38 wk)	Open fetal surgery does not improve survival over standard care
Harrison, et al (32), 1998 Prospective	Standard postnatal care (n=13) versus open fetal TO (n=13) versus fetoscopic TO (n=8)	Diagnosis <25 wk, liver herniation, LHR <1.4	Standard 38% versus open 15% versus fetoscopic 75%	PROM in 63% of fetoscopic TO Intervention groups delivered more prematurely (37 wk standard, 30 wk open, 32 wk fetoscopic)	Fetoscopic TO may offer benefit but not open TO
Flake, et al (33), 2000 Prospective	Open fetal TO (n=15)	Left: liver herniation, LHR ≤1.0 Right: massive liver herniation, no contralateral lung tissue	33%	2 deaths from early PTL; mean pregnancy duration after TO, 38 days (most delivered between 29 and 33 wk)	TO can result in lung growth in a subset; survival compromised by abnormal lung function and prematurity
Harrison, et al (34), 2003 Prospective, randomized	Fetal TO (n=11) versus standard care (n=13)	Left-sided, liver herniation, LHR <1.4	73% versus 77% (P=1.00)	PROM and PTD more common in fetal TO (31 wk TO, 37 wk standard, P<0.001)	No improvement in survival or morbidity
Jani, et al (35), 2009 Prospective, multicenter	FETO (n=210)	Liver herniation, LHR ≤1.0	48%	PPROM in 47%; median delivery at 35 wk, 31% born <34 wk	FETO associated with high rate of PROM and PTD but improvement in estimated survival

CDH=congenital diaphragmatic hernia, FETO=fetal endoscopic tracheal occlusion, LHR=lung-to-head ratio, PROM=premature rupture of membranes, PPROM=preterm premature rupture of membranes, PTD=preterm delivery, PTL=preterm labor, TO=tracheal occlusion

tropic support. Notably, if the liver is in the chest, the venous catheter is unlikely to pass through the ductus venosus, in which case alternate central venous access must be sought. Plain films of the chest and abdomen should be obtained.

Maintenance of a quiet environment, use of infant earmuffs, and judicious administration of sedation may help to decrease the physiologic lability associated with PPHN. The utility of paralytic agents in CDH remains controversial. Some experts believe paralysis promotes atelectasis of dependent lung regions, thereby increasing ventilation-perfusion mismatch. (37) Paralysis may also increase peripheral edema and decrease chest wall compliance. (38) On the other hand, neuromuscular blockade often helps to improve oxygenation and ventilation. (39) Its role in the management of CDH is typically individualized according to center practices.

Cardiorespiratory Management: Ventilation

The primary goal of mechanical ventilation in the infant who has CDH is to minimize injury to existing lung tissue by using the lowest possible peak pressures (ideally ≤25 cm H_2O) while allowing adequate gas exchange to avoid hypoxemia and acidemia. The amount of ventilator

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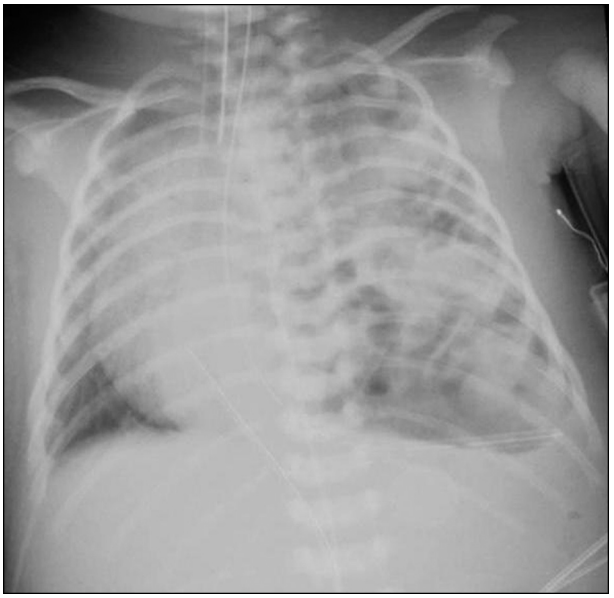

Figure. Neonatal chest radiograph showing left-sided CDH. Multiple gas-filled loops are present within the left hemithorax, and mediastinal and cardiac shift to the right is evident. The infant has umbilical arterial and venous lines in place along with endotracheal and orogastric tubes.

support an infant requires is determined by the degree of pulmonary hypoplasia, the severity of pulmonary hypertension, and the extent of postnatal lung injury. Strategies that include permissive hypercapnia (using minimal ventilator pressures and allowing higher levels of $PaCO_2$ to reduce barotrauma), early use of high-frequency ventilation, and use of ECMO for rescue have been adopted by most CDH experts to varying degrees. (40) A typical approach is to begin with conventional ventilation, and if unable to maintain acceptable oxygenation and ventilation parameters using modest inspiratory pressures, convert to high-frequency jet or oscillatory ventilation. High-frequency mechanical ventilation allows excellent gas exchange using minimal tidal volumes, theoretically reducing barotrauma. (41)

Cardiorespiratory Management: Oxygenation

Supplemental oxygen is administered to improve oxygenation. iNO, a selective pulmonary vasodilator, mediates smooth muscle relaxation by activating guanylyl cyclase, leading to production of cyclic guanosine 5'-monophosphate (cGMP), thereby improving pulmonary blood flow and augmenting gas exchange. In a recent Cochrane review, iNO was shown to reduce the need for ECMO in term infants who had respiratory failure. (42) Unfortunately, infants who had CDH did not appear to share this same benefit, possibly because of pulmonary hypoplasia and biochemical differences in the NO-cGMP pathway. Many centers offer at least a trial of iNO, with weaning of the medication if the infant does not respond.

Blood pressure support using isotonic fluids and inotropic medications is critical to maintain adequate mean arterial blood pressure and minimize right-to-left shunting across the ductus arteriosus. The administration of surfactant remains controversial. Based on animal models of CDH demonstrating surfactant deficiency, (43) some experts believe that exogenous surfactant administration is indicated in light of a probable dysfunctional surfactant system. However, a report from the Congenital Diaphragmatic Hernia Registry did not find that surfactant improves outcomes in CDH. (44) Individual centers often base decisions regarding surfactant on a case-by-case basis, according to gestational age and findings on chest radiography. (24)

Other Considerations

Echocardiography is indicated in CDH to evaluate for heart defects, assess cardiac function, and determine the presence of pulmonary hypertension. Ultrasonography of the kidneys may be warranted, based on the association between CDH and genitourinary abnormalities. Cranial ultrasonography is helpful to rule out major intracranial anomalies and is required for those being considered for ECMO to evaluate for intracranial hemorrhage. Some centers have found success using novel therapies such as milrinone for selective pulmonary vasodilation (45) and sildenafil for management of PPHN. (19)(46)

ECMO

Despite a lack of evidence demonstrating benefit in infants who have CDH, (47) ECMO is often used preoperatively as rescue therapy for infants who have severe pulmonary hypoplasia and pulmonary hypertension in the setting of failed medical management. In addition, some centers offer ECMO as a postoperative strategy for infants who deteriorate clinically following surgical repair. Details of how ECMO is performed are beyond the scope of this review. Briefly, venoarterial ECMO allows complete cardiopulmonary bypass, in contrast to venovenous ECMO, which requires the infant have sufficient intrinsic myocardial function to support oxygen delivery. Because infants who have CDH are often hemodynamically unstable, venoarterial ECMO has traditionally been the preferred mode of ECMO support. However, recent data suggest increasing use of venovenous ECMO in sick neonates. (48)

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ECMO is a temporary strategy, and its success ultimately depends on the reversibility of the underlying condition. Accordingly, many centers have adopted ECMO criteria for infants who have CDH that must be satisfied in addition to the standard ECMO exclusion criteria (major congenital or chromosomal anomalies, gestational age <34 wk, birthweight <2 kg, irreversible pulmonary disease or uncorrectable cardiac disease, severe irreversible brain injury, presence of existing intraventricular hemorrhage). The inclusion criteria often outline specific physiologic parameters the infant must meet (eg, $PaCO_2$ <65 mm Hg, preductal oxygen saturation >85%) and serve to demonstrate (albeit indirectly) the presence of sufficient lung tissue to allow survival off ECMO support. (40) Selection criteria for ECMO vary significantly among centers. (49) Among those at highest risk for ECMO are infants who have prenatally diagnosed liver herniation. (50)

In certain centers, ECMO use has decreased as gentle ventilation techniques have become more widely accepted. In others, ECMO is used even earlier, as in the ex utero intrapartum therapy (EXIT)-to-ECMO strategy, in which prenatally identified high-risk infants are placed on ECMO immediately after delivery while still connected to the placenta. (51)

Surgical Repair

Historically, CDH was considered a surgical emergency, with repair performed urgently after birth. However, a delayed surgical approach has been shown to reduce mortality, presumably by allowing time for preoperative stabilization and medical management of pulmonary hypertension. Still, the ideal time for repair remains unknown. Many surgeons delay operative intervention for up to 7 to 10 days after birth to allow maximal relaxation of the pulmonary vasculature. (40) Surgical repair is considered once an infant can maintain adequate gas exchange using low inspiratory pressures and pulmonary vascular resistance has decreased. In some centers, when high-frequency ventilation is used, surgery may be delayed until the infant tolerates the transition to conventional ventilation for at least as long as the expected duration of surgery.

Timing of repair in relation to ECMO is controversial. The primary risk of surgical repair while on ECMO is significant bleeding, but repair after decannulation may lead to recurrence of pulmonary hypertension. Many centers elect for delayed repair on ECMO following successful weaning but before decannulation, although recent data from the CDH Registry suggests that repair after ECMO is associated with the best outcomes. (52)

Depending on the size of the diaphragmatic defect, surgical repair may require placement of a prosthetic patch using Gore-tex®, Marlex, or Surgi-Sys (engineered biosynthetic porcine submucosal matrix). Some surgeons prefer to use a muscle flap from the latissimus dorsi or internal oblique and transversus abdominis muscles. Procedures that require extensive dissection are avoided in any infant who may require ECMO because of the risk of bleeding. In addition to the increased mortality risk related to patch repair, (53) major disadvantages include infection, risk of hernia recurrence, and the association with poor neurodevelopmental outcome and chest and abdominal wall deformities.

In cases where replacement of the abdominal viscera prohibits abdominal wound closure, use of a silo may be necessary, with gradual reduction of the abdominal contents over several days.

As the trend toward minimally invasive surgery has intensified, some surgeons have developed an interest in adapting these techniques to the CDH population. Although minimally invasive surgery may be appropriate in the most stable patients, particularly those who have a late presentation and adequate respiratory reserve, the risks are not inconsequential and include significant rises in $PaCO_2$ or acidemia necessitating conversion to an open procedure. (54) Further studies are needed to compare the minimally invasive approach with traditional operative management strategies for both short- and long-term outcomes.

The use of chest tubes after repair for draining accumulated fluid is no longer considered routine; rather, it is individualized based on center practices. In most cases, the fluid is gradually resorbed as the hypoplastic lung expands in the thoracic space. Therefore, chest tubes are primarily indicated in the case of active bleeding or air leak.

Table 2 outlines important management considerations in the postnatal treatment of infants with CDH.

Outcomes in CDH Survivors

As infants who have CDH continue to survive beyond the neonatal period, the focus of much clinical research has shifted toward reducing survivor morbidity. Long-term morbidity is highest in those who require patch repair and those treated with ECMO. Whether this is reflective of more severe primary disease or due to a greater number of associated complications remains a subject of debate. In fact, multiple complex factors likely contribute to long-term morbidity, including perinatal, perioperative, and other postnatal events.

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Table 2. Postnatal Treatment of Congenital Diaphragmatic Hernia*

Treatment in the Delivery Room

- No bag masking
- Immediate intubation
- Peak pressure <25 cm H_2O
- Nasogastric tube

Treatment in the NICU/PICU

- Adapt ventilation to obtain preductal saturation between 85% and 95%
- pH >7.20, lactate 27.0 to 45.0 mg/dL (3 to 5 mmol/L)
- CMV or HFOV; maximum peak pressure of 25 to 28 cm H_2O in CMV and mean airway pressure of 17 cm H_2O in HFOV
- Target blood pressure: normal value for gestational age
- Consider inotropic support

Treatment of PH

- Perform echocardiography
- iNO is the first choice; in case of nonresponse, stop iNO
- In the chronic phase: phosphodiesterase inhibitors, endothelin antagonist, tyrosine kinase inhibitors

ECMO

- Only start if the patient is able to achieve a preductal saturation >85%
- Inability to maintain preductal saturation >85%
- Respiratory acidosis
- Inadequate oxygen delivery (lactate > 45.0 mg/dL [5 mmol/L])
- Therapy-resistant hypotension

Surgical Repair

- Fio_2 <0.5
- Mean blood pressure normal for gestational age
- Urine output >2 mL/kg per hour
- No signs of persistent PH

*Based on the consensus statement of the European Congenital Diaphragmatic Hernia Consortium. CMV=conventional mechanical ventilation, ECMO=extracorporeal membrane oxygenation, Fio_2=fraction of inspired oxygen, HFOV=high-frequency oscillatory ventilation, iNO=inhaled nitric oxide, NICU=neonatal intensive care unit, PH=pulmonary hypertension, PICU=pediatric intensive care unit

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Chronic Lung Disease and Reactive Airway Disease

Up to 50% of CDH survivors develop long-term pulmonary sequelae, including chronic lung disease, reactive airway disease, recurrent respiratory infections, and persistent pulmonary hypertension. (3)(55)(56) The degree of pulmonary morbidity varies and is not only dependent on the degree of pulmonary underdevelopment but also on the severity of iatrogenic injury that the lungs incurred in the neonatal period. Patch repair and ECMO are also associated with long-term respiratory complications. (2)(57) One study found that 16% of CDH survivors required supplemental oxygen at discharge; (2) in other reports, this number was closer to 40% to 50%. (10)(58) A significant percentage of patients are discharged from the hospital on diuretic and bronchodilator therapy. Approximately 25% of infants demonstrate evidence of obstructive airway disease, (57) with up to 50% of survivors showing asthmalike symptoms during childhood. Bronchodilators and inhaled corticosteroids are prescribed for most patients during the first year after birth. (2) In addition, up to 4% of infants require tracheostomy for respiratory failure. (56)(57) Lung function abnormalities appear to improve over time as compensatory lung growth occurs, although these data are limited to a relatively small number of patients. (3)(59) As with all children who have chronic lung disease, prophylaxis against respiratory syncytial virus is critical.

Pulmonary Hypertension

Chronic pulmonary hypertension is one of the major complicating factors in CDH, with overall mortality attributable to pulmonary hypertension approaching 50%. (60)(61) Management strategies for infants who do not require mechanical ventilation but have PPHN include iNO delivered via nasal cannula and oral sildenafil, a highly selective phosphodiesterase inhibitor type 5. Sildenafil has been used to treat pulmonary hypertension in older children and adults (62) by limiting degradation of cGMP and thereby enhancing endogenous nitric oxide activity. (63) Results from a recent study indicate sildenafil may augment cardiac output in infants who have CDH during the first 2 weeks of administration. (46) Further studies of CDH survivors are needed to investigate the natural course of pulmonary hypertension in these patients as well as the optimal dosing, timing, and indications for sildenafil.

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Gastroesophageal Reflux, Feeding Difficulties, and Failure to Thrive

Numerous studies have documented the high incidence of GER in infants and children who have CDH. (4)(6) Several mechanisms have been proposed, including fetal esophageal obstruction resulting in impaired esophageal motility, shortened esophageal length, disruption of the angle of His due to the abnormal location of the stomach in utero, and complete or partial absence of the parahiatal diaphragm. Although many CDH survivors can be treated successfully with medical treatment, a significant number (up to 23% in one series (5)) have severe GER that requires surgical intervention, namely, fundoplication. Factors associated with need for fundoplication are patch repair, ECMO treatment, and intrathoracic liver position. (5)(64)

Protracted hospitalization combined with symptoms of GER and delayed initiation of oral feedings contributes to the development of oral aversion in infants who have CDH. Many require supplementation with enteral tube feedings, either via a nasogastric or gastrostomy feeding tube. In conjunction with an increased metabolic demand due to pulmonary morbidity, these feeding-related problems commonly result in failure to thrive, with a significant proportion of infants remaining below the 5th percentile for weight in the first 3 postnatal years. (65)(66)(67) Catch-up growth can occur with aggressive management, (10) but poor growth remains a problem for a subset of patients.

Long-term Neurodevelopmental Outcomes

The underlying mechanisms of brain injury in CDH remain poorly defined. Chronic lung disease, postnatal growth failure, and prolonged hospitalization are factors known to affect neurodevelopment adversely. In addition, affected infants are exposed to perinatal and postnatal hypoxia, hypotension, hypercapnia, inflammation, and acidosis, all of which interfere with central nervous system development. In a study of eight CDH survivors, all had abnormalities on brain MRI, including ventricular dilatation, abnormal signal in the white matter and basal ganglia, and abnormal myelination of the posterior limb of the internal capsule. (68) In another study, survivors who had motor problems at age 1 year were more likely to have abnormal findings on neuroimaging, continued respiratory compromise at age 1 year, and a history of longer duration of mechanical ventilation. (69)

Most studies examining the long-term neurodevelopmental outcomes of CDH survivors have focused on the 18- to 36-month follow up period, with a considerable paucity of information describing the longer-term sequelae. In addition, few studies detail the neurodevelopmental outcome of CDH survivors *not* treated with ECMO. Only recently have studies begun to describe the developmental and psychological outcomes of survivors in late childhood and adolescence. One such series looking at non-ECMO-treated CDH survivors between 8 and 12 years of age found only 54% to be functioning cognitively at expected school level. (7) Investigators also noted a higher prevalence of emotional and behavioral problems among CDH survivors compared with the general population. Poor neurodevelopmental outcome in infants who have CDH is likely the result of a combination of multiple complex factors. Therefore, all CDH survivors should be considered at risk for cognitive delay and be followed regularly in a multidisciplinary clinic.

Neurodevelopmental Outcome in CDH ECMO Survivors

The relationship between infants in whom CDH is treated with ECMO and adverse neurocognitive outcomes remains controversial. The physiologic basis for ECMO treatment leading to cognitive delay rests on several factors. First, infants who require ECMO to survive represent the sickest subset of patients in the NICU. They are at significant risk for hypoxia and hypoperfusion before and during ECMO treatment (56) and, therefore, are fundamentally subject to hypoxic-ischemic brain injury. Furthermore, ECMO support requires systemic anticoagulation (in all) and ligation of the carotid artery (in venoarterial). The increase in neurologic complications in infants treated with venoarterial ECMO (seizures, cerebral infarction) may be attributed to decreased cerebral blood flow resulting from ligation of the right internal carotid artery. (70) Some have shown that venovenous ECMO may be sufficient to support CDH patients, and when compared with venoarterial ECMO, is associated with decreased risk of neurologic impairment. (48)

One study of CDH ECMO survivors found 19% to have severe neurodevelopmental problems (defined as speech, language, or motor delay) at a median age of 5 years. (71) In this report, only 25% of survivors were free of significant neurodevelopmental deficit at follow-up. A recent study of infants prospectively enrolled in an interdisciplinary follow-up program found 46% of CDH ECMO survivors had deficits in developmental outcome as well as an increased risk for psychomotor dysfunction and motor delays. (72) Hence, some experts conclude that although ECMO can support the most critically ill CDH infants, its use is associated with significant mor-

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Table 3. **Recommended Schedule of Follow-up Evaluations for Infants Who Have Congenital Diaphragmatic Hernia**

	Before Discharge	1 to 3 Months After Birth	4 to 6 Months After Birth	9 to 12 Months After Birth	15 to 18 Months After Birth	Annual Through 16 Years
Weight, length, occipitofrontal circumference	X	X	X	X	X	X
Chest radiograph	X	If patched	If patched	If patched	If patched	If patched
Pulmonary function testing			If indicated		If indicated	If indicated
Childhood immunizations	As indicated throughout childhood	X	X	X	X	X
RSV prophylaxis	RSV season during first 2 years after birth (if evidence of chronic lung disease)		X	X	X	X
Echocardiography and cardiology follow-up	X	If previously abnormal or on supplemental oxygen	If previously abnormal or on supplemental oxygen	If previously abnormal or on supplemental oxygen	If previously abnormal or on supplemental oxygen	If previously abnormal or on supplemental oxygen
Head CT scan or MRI	If 1) abnormal finding on head ultrasonography, 2) seizures/abnormal neurologic findings, or 3) ECMO or patch repair	As indicated	As indicated	As indicated	As indicated	As indicated
Hearing evaluation	Auditory brainstem evoked response or otoacoustic emissions screen	X	X	X	X	Every 6 months to age 3 years, then annually to age 5 years
Developmental screening evaluation	X	X	X	X		Annually to age 5 years
Neurodevelopmental evaluation	X			X		Annually to age 5 years
Assessment for oral feeding problems	X	X	If oral feeding problems	If oral feeding problems	If oral feeding problems	If oral feeding problems
Upper gastrointestinal study, pH probe, or gastric scintiscan	Consider for all patients	If symptoms	If symptoms	Consider for all patients	If symptoms	If symptoms
Esophagoscopy		If symptoms	If symptoms	If symptoms or if abnormal gastrointestinal evaluations	If symptoms	If symptoms

(continued)

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Table 3. Recommended Schedule of Follow-up Evaluations for Infants Who Have Congenital Diaphragmatic Hernia—Continued

	Before Discharge	1 to 3 Months After Birth	4 to 6 Months After Birth	9 to 12 Months After Birth	15 to 18 Months After Birth	Annual Through 16 Years
Scoliosis and chest wall deformity screening (physical examination, chest radiograph, or CT scan of the chest)				X		X

RSV=respiratory syncytial virus, CT=computed tomography, MRI=magnetic resonance imaging, ECMO=extracorporeal membrane oxygenation
The neurosensory tests performed and frequency of surveillance may differ among infants because of variability in neurologic, developmental, and physiologic impairments. Follow-up should be tailored to each infant.
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tality and long-term morbidity. (71) In contrast, others have not found ECMO to be associated with poor neurodevelopmental outcome in CDH infants. (57)(73) Further studies are needed to answer this important question definitively.

Sensorineural Hearing Loss

Infants who have CDH are known to be at high risk of sensorineural hearing loss (up to 60% in one case series), the degree of which has only recently become better understood. (8) This type of hearing loss is progressive, and repeated hearing screening at 6-month intervals throughout infancy and early childhood is indicated to prevent significant speech and language delay. Along with hypoxia and ECMO treatment, ototoxic medications commonly used in the NICU (aminoglycoside antibiotics, loop diuretics, neuromuscular blocking agents) contribute to this problem. (8)

Surgical Morbidity

The incidence of reherniation is directly related to the use of synthetic patch repair and ranges from 5% to 80%. (66)(74) Timing of reherniation varies from months to years after initial repair. Presenting symptoms may include gastrointestinal (feeding difficulties, vomiting) and respiratory (coughing, wheezing), or there may be no symptoms. Thus, surveillance chest radiographs obtained at regular intervals are advised. (55)(74)

Almost invariably, infants who have CDH have intestinal malrotation. Consequently, some survivors develop intestinal obstruction due to midgut volvulus or adhesions. This complication can be life-threatening if not recognized and treated in a timely manner.

Chest wall and spinal deformities occur commonly in survivors of CDH. (65) One study of adult survivors found 48% with chest asymmetry, 18% with pectus excavatum, and 27% with significant scoliosis. (75) The incidence increases with a larger diaphragmatic defect, presumably because repair of a large defect puts tension on the spine and interferes with normal development of the thorax. Other contributing factors include a smaller thoracic cavity on the affected side and increased work of breathing leading to development of a pectus abnormality via retraction of the cartilaginous anterior chest wall. For the most part, these deformities are mild and surgery is rarely required, although the exact relationship between chest wall deformities and impaired pulmonary function remains unclear.

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Patient Monitoring

CDH survivors require long-term periodic follow-up evaluation by a multidisciplinary team to identify and effectively treat potential challenges. The goal is early and appropriate intervention to prevent additional disability and maximize developmental and cognitive outcomes. An article from the Section on Surgery and the Committee on Fetus and Newborn of the American Academy of Pediatrics advises that children who have CDH be followed into early childhood and tested to be sure that they are healthy and developing to the best of their potential. (55) The Academy recommends specific medical tests as standard of care for CDH survivors, including annual neurodevelopmental screening and evaluation through early school age (Table 3). In addition, the guidelines emphasize the importance of continued medical and developmental follow-up for CDH survivors.

Conclusion

CDH is the result of a simple anatomic defect that leads to a complex pathophysiology with lasting implications for affected infants and their families. Advancements in pediatric surgery and neonatal intensive care have led to improved overall survival of infants who have CDH in high-volume centers, but at the expense of increased long-term morbidity in infants who previously would have died. Research is ongoing, particularly in search of an in utero cure for CDH. The challenge for those who care for these fascinating yet formidable patients is how to achieve the highest survival rates for infants while ensuring the best possible long-term functional outcomes in survivors. The answer lies not only in the endorsement of research endeavors that may lead to the development of novel therapies and treatment strategies, but also in continual examination of how practices in the NICU translate into real-life experiences for patients and their families.

American Board of Pediatrics Neonatal-Perinatal Content Specifications

- Plan appropriate therapy for an infant with extrapulmonary causes of respiratory distress.
- Recognize the clinical features of extrapulmonary causes of respiratory distress.
- Recognize the imaging features of extrapulmonary causes of respiratory distress.
- Know the indications, techniques, effects, and risks of extracorporeal membrane oxygenation (ECMO).

References

1. Hislop A, Reid L. Persistent hypoplasia of the lung after repair of congenital diaphragmatic hernia. *Thorax*. 1976;31:450–455
2. Muratore CS, Kharasch V, Lund DP, et al. Pulmonary morbidity in 100 survivors of congenital diaphragmatic hernia monitored in a multidisciplinary clinic. *J Pediatr Surg*. 2001;36:133–140
3. Trachsel D, Selvadurai H, Bohn D, Langr JC, Coates AL. Long-term pulmonary morbidity in survivors of congenital diaphragmatic hernia. *Pediatr Pulmonol*. 2005;39:433–439
4. Muratore CS, Utter S, Jaksic T, Lund DP, Wilson JM. Nutritional morbidity in survivors of congenital diaphragmatic hernia. *J Pediatr Surg*. 2001;36:1171–1176
5. Su W, Berry M, Puligandla PS, Aspirot A, Flageole H, Laberge JM. Predictors of gastroesophageal reflux in neonates with congenital diaphragmatic hernia. *J Pediatr Surg*. 2007;42:1639–1643
6. Fasching G, Huber A, Uray E, Sorantin E, Lindbichler F, Mayr J. Gastroesophageal reflux and diaphragmatic motility after repair of congenital diaphragmatic hernia. *Eur J Pediatr Surg*. 2000;10:360–364
7. Bouman NH, Koot HM, Tibboel D, Hazebroek FW. Children with congenital diaphragmatic hernia are at risk for lower levels of cognitive functioning and increased emotional and behavioral problems. *Eur J Pediatr Surg*. 2000;10:3–7
8. Morini F, Capolupo I, Masi R, et al. Hearing impairment in congenital diaphragmatic hernia: the inaudible and noiseless foot of time. *J Pediatr Surg*. 2008;43:380–384
9. Peetsold MG, Huisman J, Hofman VE, Heij HA, Raat H, Gernke RJ. Psychological outcome and quality of life in children born with congenital diaphragmatic hernia. *Arch Dis Child*. 2009;94:834–840
10. Cortes RA, Keller RL, Townsend T, et al. Survival of severe congenital diaphragmatic hernia has morbid consequences. *J Pediatr Surg*. 2005;40:36–46
11. Langham MR Jr, Kays DW, Ledbetter DJ, Frentzen B, Sanford LL, Richards DS. Congenital diaphragmatic hernia. Epidemiology and outcome. *Clin Perinatol*. 1996;23:671–688
12. Stege G, Fenton A, Jaffray B. Nihilism in the 1990s: the true mortality of congenital diaphragmatic hernia. *Pediatrics*. 2003;112:532–535
13. Fisher JC, Jefferson RA, Arkovitz MS, Stolar CJ. Redefining outcomes in right congenital diaphragmatic hernia. *J Pediatr Surg*. 2008;43:373–379
14. Skarsgard ED, Harrison MR. Congenital diaphragmatic hernia: the surgeon's perspective. *Pediatr Rev*. 1999;20:e71–e78
15. Sweed Y, Puri P. Congenital diaphragmatic hernia: influence of associated malformations on survival. *Arch Dis Child*. 1993;69:68–70
16. Harrison MR, Adzick NS, Estes JM, Howell LJ. A prospective study of the outcome for fetuses with diaphragmatic hernia. *JAMA*. 1994;271:382–384
17. Tsao K, Allison ND, Harting MT, Lally PA, Lally KP. Congenital diaphragmatic hernia in the preterm infant. *Surgery*. 2010;148:404–410
18. Estimating disease severity of congenital diaphragmatic hernia in the first 5 minutes of life. The Congenital Diaphragmatic Hernia Study Group. *J Pediatr Surg*. 2001;36:141–145
19. Rocha GM, Bianchi RF, Severo M, et al. Congenital diaphragmatic hernia. The post-neonatal period part II. *Eur J Pediatr Surg*. 2008;18:307–312
20. Downard CD, Jaksic T, Garza JJ, et al. Analysis of an improved

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survival rate for congenital diaphragmatic hernia. *J Pediatr Surg.* 2003;38:729–732
21. Chiu PP, Sauer C, Mihailovic A, et al. The price of success in the management of congenital diaphragmatic hernia: is improved survival accompanied by an increase in long-term morbidity? *J Pediatr Surg.* 2006;41:888–892
22. Bagolan P, Casaccia G, Crescenzi F, Nahom A, Trucchi A, Giorlandino C. Impact of a current treatment protocol on outcome of high-risk congenital diaphragmatic hernia. *J Pediatr Surg.* 2004; 39:313–318
23. Levison J, Halliday R, Holland AJ, et al. A population-based study of congenital diaphragmatic hernia outcome in New South Wales and the Australian Capital Territory, Australia, 1992–2001. *J Pediatr Surg.* 2006;41:1049–1053
24. Hedrick HL. Management of prenatally diagnosed congenital diaphragmatic hernia. *Semin Fetal Neonat Med.* 2010;15:21–27
25. Albanese CT, Lopoo J, Goldstein RB, et al. Fetal liver position and perinatal outcome for congenital diaphragmatic hernia. *Prenat Diagn.* 1998;18:1138–1142
26. Adzick NS, Outwater KM, Harrison MR, et al. Correction of congenital diaphragmatic hernia in utero. IV. An early gestational fetal lamb model for pulmonary vascular morphometric analysis. *J Pediatr Surg.* 1985;20:673–680
27. Harrison MR, Adzick NS, Flake AW, et al. Correction of congenital diaphragmatic hernia in utero. VI. Hard-earned lessons. *J Pediatr Surg.* 1993;28:1411–1418
28. Harding R, Hooper SB. Regulation of lung expansion and lung growth before birth. *J Appl Physiol.* 1996;81:209–224
29. Bratu I, Flageole H, Laberge JM, Chen MF, Piedboeuf B. Pulmonary structural maturation and pulmonary artery remodeling after reversible fetal ovine tracheal occlusion in diaphragmatic hernia. *J Pediatr Surg.* 2001;36:739–744
30. DiFiore JW, Fauza DO, Slavin R, Peters CA, Fackler JS, Wilson JM. Experimental fetal tracheal ligation reverses the structural and physiological effects of pulmonary hypoplasia in congenital diaphragmatic hernia. *J Pediatr Surg.* 1994;29:248–257
31. Harrison, MR, Mychaliska GB, Alanese CT, et al. Correction of congenital diaphragmatic hernia in utero. VII. A prospective trial. *J Pediatr Surg.* 1997;32:1637–1642
32. Harrison MR, Myshcaliska GB, Albanese CT, et al. Correction of congenital diaphragmatic hernia in utero. IX. Fetuses with poor prognosis (liver herniation and low lung-to-head ratio) can be saved by fetoscopic temporary tracheal occlusion. *J Pediatr Surg.* 1998; 33:1017–1023
33. Flake AW, Crombleholme TM, Johnson MP, Howell LJ, Adzick NS. Treatment of severe congenital diaphragmatic hernia by fetal tracheal occlusion: clinical experience with fifteen cases. *Am J Obst Gynecol.* 2000;183:1059–1066
34. Harrison MR, Keller RL, Hawgood SB, et al. A randomized trial of fetal endoscopic tracheal occlusion for severe fetal congenital diaphragmatic hernia. *N Engl J Med.* 2003;349:1916–1924
35. Jani JC, Nicolaides KH, Garatacos E, et al. Severe diaphragmatic hernia treated by fetal endoscopic tracheal occlusion. *Ultrasound Obstet Gynecol.* 2009;34:304–310
36. Reiss I, Schaible T, van den Hout L, et al. Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: the CDH EURO Consortium consensus. *Neonatology.* 2010;98:354–364
37. Tokics L, Hedenstierna G, Svensson L, et al. $\dot{V}/\dot{Q}$ distribution and correlation to atelectasis in anesthetized paralyzed humans. *J Appl Physiol.* 1996;81:1822–1833
38. Bhutani VK, Abbasi S, Sivieri EM. Continuous skeletal muscle paralysis: effect on neonatal pulmonary mechanics. *Pediatrics.* 1988;81:419–422
39. Henry WG, Stevens DC, Schreiner RL, Grosfeld JL, Ballantine TV. Respiratory paralysis to improve oxygenation and mortality in large newborn infants with respiratory distress. *J Pediatr Surg.* 1979;14:761–767
40. Logan JW, Rice HE, Goldberg RN, Cotten CM. Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. *J Perinatol.* 2007;27:535–549
41. Kuluz MA, Smith PB, Mears SP, et al. Preliminary observations of the use of high-frequency jet ventilation as rescue therapy in infants with congenital diaphragmatic hernia. *J Pediatr Surg.* 2010; 45:698–702
42. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev.* 2010;12: CD000509
43. Glick PL, Stannard VA, Leach CL, et al. Pathophysiology of congenital diaphragmatic hernia II: The fetal lamb CDH model is surfactant deficient. *J Pediatr Surg.* 1992;27:382–388
44. Van Meurs K; Congenital Diaphragmatic Hernia Study. Is surfactant therapy beneficial in the treatment of the term newborn infant with congenital diaphragmatic hernia? *J Pediatr.* 2004;145: 312–316
45. McNamara PJ, Laigue F, Muang-In S, Whyte HE. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. *J Crit Care.* 2006;21:217–222
46. Noori S, Friedlich P, Wong P, Garingo A, Seri I. Cardiovascular effects of sildenafil in neonates and infants with congenital diaphragmatic hernia and pulmonary hypertension. *Neonatology.* 2007;91:92–100
47. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet.* 1996;348:75–82
48. Guner YS, Khemani RG, Quereshi FG, et al. Outcome analysis of neonates with congenital diaphragmatic hernia treated with venovenous vs venoarterial extracorporeal membrane oxygenation. *J Pediatr Surg.* 2009;44:1691–1701
49. Chapman RL, Peterec SM, Bizzarro MJ, Mercurio MR. Patient selection for neonatal extracorporeal membrane oxygenation: beyond severity of illness. *J Perinatol.* 2009;29:606–611
50. Hedrick HL, Danzer E, Merchant A, et al. Liver position and lung-to-head ratio for prediction of extracorporeal membrane oxygenation and survival in isolated left congenital diaphragmatic hernia. *Am J Obstet Gynecol.* 2007;197:422.e1–4
51. Kunisaki SM, Barnewolt CE, Estroff JA, et al. Ex utero intrapartum treatment with extracorporeal membrane oxygenation for severe congenital diaphragmatic hernia. *J Pediatr Surg.* 2007;42: 98–106
52. Bryner BS, West BT, Hirschl RB, et al. Congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: does timing of repair matter? *J Pediatr Surg.* 2009;44:1165–1172
53. The Congenital Diaphragmatic Hernia Study Group. Defect size determines survival in infants with congenital diaphragmatic hernia. *Pediatrics.* 2007;120:e651–e657
54. Arca MJ, Barnhart DC, Lelli JL Jr, et al. Early experience with minimally invasive repair of congenital diaphragmatic hernias: results and lessons learned. *J Pediatr Surg.* 2003;38:1563–1568
55. Lally KP, Engle W. Postdischarge follow-up of infants with congenital diaphragmatic hernia. *Pediatrics.* 2008;121:627–632
56. Bagolan P, Morini F. Long-term follow up of infants with

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congenital diaphragmatic hernia. *Semin Pediatr Surg.* 2007;16:134–144
57. Jaillard SM, Pierrat V, Dubois A, et al. Outcome at 2 years of infants with congenital diaphragmatic hernia: a population-based study. *Ann Thorac Surg.* 2003;75:250–256
58. Colby CE. Surfactant replacement therapy on ECMO does not improve outcome in neonates with congenital diaphragmatic hernia. *J Pediatr Surg.* 2004;39:1632–1637
59. Peetsold MG, Vonk-Noordegraaf A, Heij HH, Gemke RJ. Pulmonary function and exercise testing in adult survivors of congenital diaphragmatic hernia. *Pediatr Pulmonol.* 2007;42:325–331
60. Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr.* 1997;131:55–62
61. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. The Neonatal Inhaled Nitric Oxide Study Group (NINOS). *Pediatrics.* 1997;99:838–845
62. Wilkens H, Guth A, Konig J, et al. Effect of inhaled iloprost plus oral sildenafil in patients with primary pulmonary hypertension. *Circulation.* 2001;104:1218–1222
63. Tulloh R. Etiology, diagnosis, and pharmacologic treatment of pediatric pulmonary hypertension. *Paediatr Drugs.* 2009;11:115–128
64. Diamond IR, Mah K, Kim PC, Bohn D, Gerstle JT, Wales PW. Predicting the need for fundoplication at the time of congenital diaphragmatic hernia repair. *J Pediatr Surg.* 2007;42:1066–1070
65. Lund DP, Mitchell J, Kharasch V, Quigley S, Kuehn M, Wilson JM. Congenital diaphragmatic hernia: the hidden morbidity. *J Pediatr Surg.* 1994;29:258–264
66. Van Meurs KP, Robbins ST, Reed VL, et al. Congenital diaphragmatic hernia: long-term outcome in neonates treated with extracorporeal membrane oxygenation. *J Pediatr.* 1993;122:893–899
67. Kamata S, Usui N, Kamiyama M, et al. Long-term follow-up of patients with high-risk congenital diaphragmatic hernia. *J Pediatr Surg.* 2005;40:1833–1838
68. Hunt RW, Kean MJ, Stewart MJ, Inder TE. Patterns of cerebral injury in a series of infants with congenital diaphragmatic hernia utilizing magnetic resonance imaging. *J Pediatr Surg.* 2004;39:31–36
69. Tracy S, Estroff J, Valim C, Friedman S, Chen C. Abnormal neuroimaging and neurodevelopmental findings in a cohort of antenatally diagnosed congenital diaphragmatic hernia survivors. *J Pediatr Surg.* 2010;45:958–965
70. Dimmitt RA, Moss RL, Rhine WD, Benitz WE, Henry MC, Vanmeurs KP. Venoarterial versus venovenous extracorporeal membrane oxygenation in congenital diaphragmatic hernia: the extracorporeal life support organization registry, 1990–1999. *J Pediatr Surg.* 2001;36:1199–1204
71. Davis PJ, Firmin RK, Mantelkow B, et al. Long-term outcome following extracorporeal membrane oxygenation for congenital diaphragmatic hernia: the UK experience. *J Pediatr.* 2004;144:309–315
72. Danzer E, Gerdes M, Bernbaum J, et al. Neurodevelopmental outcome of infants with congenital diaphragmatic hernia prospectively enrolled in an interdisciplinary follow-up program. *J Pediatr Surg.* 2010;45:1759–1766
73. Nield T. Neurodevelopmental outcome at 3.5 years of age in children treated with extracorporeal life support: relationship to primary diagnosis. *J Pediatr.* 2000;136:338–344
74. Moss RL, Chen CM, Harrison MR. Prosthetic patch durability in congenital diaphragmatic hernia: a long-term follow-up study. *J Pediatr Surg.* 2001;36:152–154
75. Vanamo K, Peltonen J, Rinatala R, Lindahl H, Jaaskelainen J, Louhimo I. Chest wall and spinal deformities in adults with congenital diaphragmatic defects. *J Pediatr Surg.* 1996;31:851–854

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NeoReviews Quiz

4. Congenital diaphragmatic hernia (CDH) occurs as an isolated abnormality in approximately 50% to 60% of cases. In the remainder, CDH, referred to as syndromic or complex CDH, is coupled with chromosomal abnormalities or other major developmental malformations. Of the following, the *most* common developmental malformation in syndromic or complex CDH is:

   A. Cardiac.
   B. Gastrointestinal.
   C. Hepatobiliary.
   D. Neurologic.
   E. Renal.

5. CDH is estimated to occur in 1 of every 3,000 live births. The epidemiology has been the subject of research of several population studies. Of the following, the *most* accurate statement regarding the epidemiology of CDH is that:

   A. CDH is a prominent feature of Turner syndrome.
   B. CDH is more common in male infants.
   C. Early prenatal diagnosis is associated with poor outcome.
   D. Left-sided defects are associated with a higher mortality.
   E. The defect is anterior (Morgagni type) in most cases.

6. Using fetal ultrasonography, the gold-standard technique for antenatal diagnosis, most cases of CDH are identified before birth. Of the following, the *most* common gestational age range for the antenatal diagnosis of CDH is:

   A. 12 to 20 weeks.
   B. 16 to 24 weeks.
   C. 20 to 28 weeks.
   D. 24 to 32 weeks.
   E. 28 to 36 weeks.

7. Most survivors of CDH have long-term respiratory problems, including chronic lung disease, reactive airway disease, and pulmonary hypertension. The difficulties that such survivors experience, however, extend beyond the respiratory system. Of the following, the *most* common diagnosis among survivors of CDH is:

   A. Behavioral disorder.
   B. Chest wall deformity.
   C. Gastroesophageal reflux.
   D. Hearing impairment.
   E. Neurocognitive delay.

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Congenital Diaphragmatic Hernia: Updates and Outcomes

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