The management and treatment of posterolateral congenital diaphragmatic hernia (CDH) remains a challenge for pediatric surgeons. Despite tremendous advances in prenatal diagnosis, surgical treatment, and neonatal critical care, CDH remains a significant cause of mortality and long-term disability. The clinical challenges lie in the broad spectrum of disease and the relative small volume of patients at individual institutions, resulting in a limited experience with the most severe CDH infants. Although some institutions have become leaders in the treatment, management, and research of CDH, the vast majority will treat fewer than 10 infants with CDH per year. Thus, broad clinical experience is difficult to achieve.

In 1946, Gross reported the first successful repair of CDH in an infant younger than 24 hours old. CDH was considered a surgical emergency, and immediate repair was the practice at that time, with excellent survival rates of greater than 90%. Since then, it has become apparent that such survival rates only included infants who lived to have an operation and did not include those who died before birth or soon thereafter. Accounting for this “hidden mortality” of CDH, actual survival may be closer to 50%.

Although surgical intervention is necessary to repair a CDH, the most recent advances have been in nonsurgical therapies. Lung-protective ventilator strategies, extracorporeal membrane oxygenation (ECMO), and preoperative stabilization before surgery have all led to a significant decrease in mortality. In addition, improved understanding of pulmonary hypoplasia and hypertension associated with CDH has led to innovative therapies.

**EPIDEMIOLOGY**

The incidence of CDH has been reported between 1 in 2000 to 5000 births. In the United States, approximately 1000 infants are born with CDH with a prevalence of 2.4 per 10,000 live births. The incidence in stillborn infants is less clear. An estimated one third of infants with CDH are stillborn and often have other associated congenital anomalies. Presumed to have the most severe form of CDH, infants who die in utero contribute to the “hidden mortality” of the disorder.

Isolated CDH infants are typically male with one third having a major congenital anomaly. However, when stillbirths are included, females with CDH tend to be more prevalent than males. Approximately 80% of CDHs are left sided. Bilateral defects are rare and are often associated with other major anomalies.

Although the exact cause remains unknown, mothers who are thin or underweight may have an increased risk of bearing an infant with CDH.

**GENETICS**

Once thought to be only a sporadic isolated anomaly, it is becoming increasingly understood that genetics plays an important role in the development of CDH. A first-degree relative has an expected disease rate of approximately 2%. Several structural chromosomal abnormalities including deletions, translocations, and trisomies have been identified. Genetic abnormalities associated with CDH include both anomalies of chromosome number (Turner’s syndrome; trisomies 13, 18, 21, 22, and 23) and conditions with specific chromosomal aberrations (i.e., 15q24-q26 deletions).

A gene distal to the 15q21 locus may be important for normal development of the diaphragm. Several specific genes have been implicated in the development of CDH based on human and animal studies, including chick ovalbumin upstream promoter-transcription factor II (COUP-TFII), Wilms’ tumor 1 gene (WT1), homolog of Drosophila slit 3 (SLIT3), and Friend of GATA2 (FOG2). CDH may present as an isolated defect or in association with other non–CDH-related anomalies. Several associated anomalies such as lung hypoplasia, intestinal...
malrotation, some cardiac malformations, and patent ductus arteriosus are considered to be sequelae of isolated CDH. Non–CDH-related defects involving the cardiovascular, central nervous, gastrointestinal, and genitourinary systems may be a consequence of an underlying field defect of unknown etiology. Non–hernia-related anomalies associated with CDH have been estimated to occur in 40% to 60% of cases.\(^\text{22,23}\)

CDH has been associated with over 50 syndromes.\(^\text{24}\)

In some cases, the diaphragmatic malformation is the predominant defect as in Fryns and Donnai-Barrow syndromes, in which CDH occurs in a high proportion of these patients.\(^\text{25,26}\)

In other cases, diaphragmatic defects occur in a small percentage but are still greater than the general population as in Simpson-Golabi-Behmel and Beckwith-Wiedemann syndromes. The inheritance patterns for these syndromes include dominant and recessive as well as autosomal and X-linked varieties.\(^\text{21}\)

Identifying the patterns of non–hernia-related anomalies with CDH and recognizing genetic syndromes are vital in determining the prognosis, treatments, counseling, and outcomes for these infants and their families.\(^\text{14,18}\)

Other syndromic patterns have been described, including Brachmann-de Lange and Pallister-Killian syndromes.\(^\text{27-29}\)

If an antenatal diagnosis of CDH is made by fetal ultrasonography, amniocentesis with karyotype and chromosomal analysis is warranted.

### ASSOCIATED ANOMALIES

The impact of associated anomalies with CDH on prognosis and outcome cannot be overstated. Ninety-five percent of stillborn infants with CDH have an associated major anomaly.\(^\text{5}\) In addition, more than 60% of infants who do not survive the immediate neonatal period have associated anomalies.\(^\text{30}\)

Of those infants who survive preoperative stabilization and come to operative repair, less than 10% have additional anomalies.\(^\text{30}\)

Although the severity of pulmonary hypoplasia and hypertension are the major determinants of overall survival, infants with CDH with another major defect have a greater morbidity and mortality. The survival advantage for infants with isolated CDH is significant compared with those with associated non–hernia-related anomalies (43.7% vs. 7.1%).\(^\text{22}\)

Because of this dismal outcome, the emphasis on detailed and accurate prenatal diagnosis has influenced the management and treatment of CDH. Twenty percent of prenatally diagnosed CDH infants have a chromosomal anomaly, with 70% having an associated structural malformation. In contrast, only 35% of postnatally diagnosed CDH infants have an associated anomaly.\(^\text{22}\)

Non–hernia-related anomalies have been associated with many different organ systems. Cardiac anomalies account for 63% of those identified.\(^\text{31}\)

Hypoplastic left ventricle with hypoplasia of the aortic arch is the most common cardiac anomaly. Often confused with hypoplastic left heart syndrome, this defect does not have the same impact as hypoplastic left heart syndrome but may exacerbate pulmonary hypertension, right-to-left shunting, and hemodynamic instability. In addition, other common cardiac defects include atrial septal defects, ventricular septal defects, and other outflow tract anomalies (transposition of the great vessels, tetralogy of Fallot, double-outlet right ventricle, and aortic coarctation).\(^\text{30,32,33}\)

In a review of 2636 infants with CDH, approximately 15% of infants had an associated cardiac defect.\(^\text{34}\)

After eliminating those lesions that were deemed hemodynamically insignificant (patent foramen ovale, atrial septal defects, patent ductus arteriosus), only 10.6% of the cohort had significant cardiac lesions in which overall survival was 41.1%, compared with the group with nonsignificant findings (70.2%).

Defects within the tracheobronchial tree have been reported, including tracheal stenosis, trifurcated trachea, and tracheal bronchus.\(^\text{35}\)

Neural tube defects are the most common central nervous system anomaly.\(^\text{36}\)

### EMBRYOLOGY

#### Diaphragm Development

The embryologic development of the human diaphragm is a combination of complex, multicellular, multiple-tissue interactions that are poorly understood. Precursors to the diaphragm begin to form during the fourth week of gestation. Historically, the diaphragm has been thought to develop from the fusion of four embryonic components: anteriorly by the septum transversum, dorsilaterally by the pleuroperitoneal folds, dorsally by the crura of the esophageal mesentery, and posteriorly by the body wall mesoderm (Fig. 24-1).\(^\text{37,38}\)

As the embryo begins to develop, the septum transversum migrates dorsally and separates the pleuropericardial cavity from the peritoneal cavity. At this point there is still a communication between the pleural and peritoneal cavities but the pleural and pericardial cavities are separated. The septum transversum interacts with the pleuropericardial folds and mesodermal tissue surrounding the developing esophagus and other foregut structures, resulting in the formation of a primitive diaphragmatic structure known as the pleuroperitoneal fold (PPF). Bound by pericardial, pleural, and peritoneal folds, the paired PPFs separate the pleuropericardial and peritoneal cavities. Eventually, the septum transversum develops into the central tendon.\(^\text{37-41}\)

Phrenic axons and myogenic cells destined for neuromuscularization migrate to the PPF and form the mature diaphragm.\(^\text{42}\)

However, the exact mechanism in which the diaphragm becomes muscularized remains poorly understood. As the PPF develops during the sixth week of gestation, the pleuroperitoneal membranes close concurrently and separate the pleural and abdominal cavities by the eighth week of gestation. Typically, the right side completes closure before the left. Historically, the primitive fetal diaphragm has been thought to become muscularized by the inner thoracic musculature as the diaphragm closes.\(^\text{43}\)

Some have suggested that the posthepatic mesenchymal tissue...
interacting with the PPF contributes to the diaphragmatic musculature development. Others implicate a progressive development of the pleuroperitoneal membrane.

An improved understanding of diaphragmatic muscularization has supported an alternative hypothesis for its embryogenesis. Inactivation of \textit{c-met}, a tyrosine kinase receptor in mice, has demonstrated that the musculature of the diaphragm has a distinct origin other than the thoracic body wall. \textit{C-met} encodes for a receptor protein that is responsible for the delamination and migration of muscle cell precursors (MPCs) from somites. The body wall theory of diaphragm muscularization is challenged by \textit{c-met} null mutant mice that have an amuscular diaphragm and a normal body wall musculature. This hypothesis is further supported by the expression of \textit{Lbx1} on diaphragmatic MPCs, a transcription factor only found on migrating MPCs and not seen on body wall myocytes. Furthermore, immunologic staining of the diaphragm musculature revealed no MPCs from the body wall. Thus, it appears that during the process of embryologic folding, a primitive diaphragmatic structure is formed, the PPF. Subsequently, the phrenic nerve and MPCs migrate from somatic origins, populate, and muscularize the newly formed PPF (Fig. 24-2). This process corresponds to week 10 of human gestation.

**Lung Development**

Fetal lung development is divided into five overlapping stages: 1. The embryonic stage of lung development begins during the 3rd week of gestation as a diverticular formation of the caudal end of the laryngotraheal groove. The primary lung buds and trachea form from this diverticulum by the 4th week, and lobar structures are seen by the 6th week.

2. The pseudo-glandular stage occurs between the 5th and 17th weeks of gestation with the formation of formal lung buds as well as the main and terminal bronchi.
3. The canalicular stage is highlighted by the development of pulmonary vessels, respiratory bronchioles, and alveolar ducts between weeks 16 and 25 of gestation. Type 1 pneumocytes begin to appear as well as the precursors for type 2 pneumocytes. At this stage, functional gas exchange is possible.

4. The sacular stage continues from 24 weeks’ gestation to term with the maturation of alveolar sacs. Airway dimensions and surfactant synthesis capabilities continue to mature as well.

5. The alveolar stage begins right after birth with the appearance of mature alveoli. This stage extends well after birth with continued increase and development of functional alveoli.

Fetal pulmonary vascular development occurs in concordance with the associated lung development and follows the pattern of airway and alveolar maturation. A functional unit known as the acinus consists of the alveoli, alveolar ducts, and respiratory bronchioles. The pulmonary vasculature develops as these units multiply and evolve during the canalicular stage. The precapillary structure consists of the trachea, major bronchi, lobar bronchi, and terminal bronchioles. The pulmonary vascular development for the preacinar is typically completed by the end of the pseudoglandular stage. In theory, any impedance to normal pulmonary development will concurrently hinder proper pulmonary vascular development.

Pulmonary development is recognized as a complex series of interlocking programmed events regulated by genetic signals, transcription factors, growth factors, and hormones. These events regulate the temporal and spatial interactions between epithelium and endothelium. Early transcription signals, such as thyroid transcription factor-1 and hepatocyte nuclear factor-3β, regulate pulmonary development from the primitive foregut mesenchyme. Other pathways of pulmonary development include Sonic hedgehog, transforming growth factor-β, Notch-delta pathway, and Wingless-Int. In addition, glucocorticoids, thyroid hormone, and retinoic acid have all been shown to regulate pulmonary organogenesis.

**PATHOGENESIS**

The development of CDH has been attributed to a defective fusion of the pleuroperitoneal membrane, to improper development of the PPF, or to a consequence of abnormal development of the posthepatic mesenchymal plate. Others suggest that the muscular defect in CDH occurs before the complete closure of the canal as a result of abnormal formation of the diaphragm or PPFs. Traditionally, herniation of abdominal viscera through the diaphragmatic hernia was thought to impair lung development secondary to direct pulmonary compression resulting in pulmonary hypoplasia. Other evidence suggests that lung hypoplasia may occur early during embryogenesis before visceral herniation. Still others have postulated a corollary theory that primary lung maldevelopment leads to the fetal diaphragmatic defect, although this is not widely accepted. This latter theory has been refuted by the transgenic mice with the Fgf10 gene. Inactivated Fgf10 null-mutant mice do not develop lung tissue but have normal diaphragms suggesting independent pathways to diaphragm and lung development. This phenomenon is also seen in humans where infants with lung agenesis have normal diaphragms.

Pulmonary hypoplasia is characterized by a decrease in bronchial divisions, bronchioles, and alveoli. The alveoli and terminal sacules exhibit abnormal septations that impair the air-capillary interface and its ability for gas exchange. At birth, the alveoli are thick walled with intra-alveolar septations. These immature alveoli have increased glycogen content leading to thickened secretions that further limit gas exchange. Animal models of CDH have demonstrated pulmonary hypoplasia with decreased levels of total lung DNA and total lung protein. In addition, the pulmonary vasculature appears to be less compliant with abnormally thick-walled arterioles. Surfactant levels are also decreased that may result in immature functioning lungs. Abnormalities in pulmonary development are not limited to the ipsilateral lung of the CDH. The contralateral lung also exhibits structural abnormalities of pulmonary hypoplasia. These sequelae are most profound in cases in which mediastinal shift leads to contralateral lung compression. This supports the theory that lung compression may be the major cause of pulmonary hypoplasia.

The understanding of abnormal pulmonary development in CDH has been widely aided by the nitrofen murine model. Nitrofen (2,4-dichloro-phenyl-p-nitrophenyl ether) is an environmental teratogen that is relatively harmless to adult mice. However, if given during pregnancy, it can cause pulmonary, cardiac, skeletal, and diaphragmatic abnormalities. Diaphragmatic defects resulting from the administration of nitrofen in mice are very similar to those seen in humans with regard to size, location, and herniation of abdominal viscera. Depending on the time of exposure during gestation, resultant pups will develop either right or left CDH. In addition, the offspring will exhibit features of pulmonary hypoplasia, including reduced airway branching, surfactant deficiency, pulmonary vascular abnormalities, and respiratory failure at birth. These mutations are the result of many alterations in developmental pathways of embryonic mice. The nitrofen model of CDH also suggests that not all of the pulmonary hypoplasia in CDH is due to lung compression. The effect of nitrofen in causing CDH is consistent with many theories that congenital anomalies are the result of environmental insults.

Other structurally similar teratogens to nitrofen have been shown to induce CDH in animal models. Bisdimine (N,N'-bis [dichloroacetyl]-1,8-octamethylenediamine) is a spermatogenesis inhibitor. BPCA (4-biphenyl carboxylic acid) is a breakdown product of a thromboxane A2 receptor antagonist. SB-210661 is a benzofuranyl urea derivative and 5-lipoxygenase inhibitor. All these agents cause similar diaphragmatic defects during the same embryologic
Prenatal Diagnosis

Owing to the wide discrepancy of disease severity and potential fetal therapies, accurate and timely prenatal diagnosis of CDH has become paramount. The diagnosis of CDH can be made by ultrasonography in 50% to 60% of pregnancies (Fig. 24-3). Typically diagnosed at 24 weeks’ gestation, CDH has been reported as early as 11 weeks’ gestation. In some tertiary medical centers, up to 93% of the neonates with CDH may have a prenatal diagnosis. Fetal ultrasound findings include polyhydramnios, bowel loops within the chest, an echogenic chest mass, and an absent or intrathoracic gastric bubble. Severe or advanced CDH may exhibit intrathoracic “liver up,” mediastinal shift, and hydrops fetalis. Although most CDH can be detected during the second trimester, some sonographic features may not be exhibited until later in pregnancy.

Independent sonographic features of CDH have not been shown to be accurate prognosticators for poor prognosis. However, two distinct features in combination have been utilized to risk stratify: (1) a low lung-to-head ratio (LHR) and (2) liver herniation into the chest. The LHR is calculated by the cross-sectional area of the contralateral lung at the level of the cardiac atria divided by the head circumference (see Fig. 24-2). Survival of CDH fetuses based on LHR has been statistically supported. In one series, there was 100% survival with LHR greater than 1.35, 61% with LHR between 1.35 and 0.6, and no survival with LHR less than 0.6. Survival based on liver herniation alone is 56%, compared with 100% survival without liver herniation. The combination of liver herniation and low LHR (LHR < 1.0) has a demonstrated 60% mortality for infants with prenatally diagnosed CDH. Although fetal ultrasonography has been adopted as the most reliable prognostic test for CDH, its wide and inconsistent utilization has created variable results among centers. An LHR of 1.0 in one institution may be consistently different than the same results in another institution. Subsequently, LHR and liver herniation as prognosticators should be approached with some caution.

Recently, fetal magnetic resonance imaging (MRI) of infants with CDH has been introduced as an adjunctive tool to evaluate fetal lung volume and liver location. MRI-based fetal lung volume has been utilized in a manner similar to fetal ultrasonography. Several studies have touted the predictive value of fetal MRI in assessing risk. Lung volumes of CDH are calculated and compared with the predicted fetal lung volumes as a ratio. When the measured-to-expected fetal lung volumes ratio is less than 25%, there is a significant decrease in postnatal survival. Fetal lung volumes predicting the need for ECMO or degree of severity are less precise. Because of the nonstandardized approach to postnatal care for infants with CDH, conclusions regarding predictive outcomes using...
all prenatal imaging modalities should be used with caution. Nonetheless, prenatal assessment can clearly identify the most severe cases.

Prenatal diagnosis in early pregnancy provides an opportunity to optimize the prenatal and postnatal care of the fetus and mother by providing accurate prenatal counseling, discussion of possible lethal intervention, and/or termination of pregnancy. Although prenatal imaging provides valuable information, it does not consider the influences of postnatal care, especially in tertiary medical centers, on survival or overall outcome.

**Clinical Presentation**

Newborns with CDH typically present with respiratory distress. Clinical scenarios may range from immediate respiratory distress with associated low Apgar scores to an initial stable period and a delay in respiratory distress for 24 to 48 hours to late presentations that may occur years into life. Initial signs include tachypnea, chest wall retractions, grunting, cyanosis, and pallor. There may be clinical signs of ongoing fetal circulation and subsequent shunting. On physical examination, infants will often have a scaphoid abdomen and an increased chest diameter. The point of maximal cardiac impulse is often displaced (contralateral to the diaphragmatic defect), suggesting mediastinal shift. Bowel sounds may be auscultated within the chest cavity with a decrease in breath sounds bilaterally. Chest excursion may be low, suggesting a lower tidal volume.

The diagnosis of CDH is typically made by chest radiography demonstrating intestinal loops within the thorax (Fig. 24-5). The location of the gastric bubble should be determined with the placement of an orogastric tube. In rare circumstances, a contrast radiograph is necessary. The abdominal cavity may have minimal to no intestinal gas. Right-sided CDH may be more difficult to diagnose (Fig. 24-6). Salient features such as intestinal and gastric herniation may not occur. Rather, features of lobar compression may be the only radiographic sign and may be confused with congenital cystic adenomatoid malformations, pulmonary sequestrations, bronchopulmonary cysts, neurogenic cysts, or cystic teratomas.

Although most infants with CDH will be diagnosed within the first 24 hours, as many as 20% may present beyond the neonatal period. These infants usually present with milder respiratory symptoms, chronic pulmonary infections, pleural effusions, pneumonias,
feeding intolerance, or gastric volvulus. Older children may present with symptoms of mediastinal compression due to acute gastric distention. Because CDH invariably causes abnormal intestinal rotation and fixation, some children may present with intestinal obstruction or volvulus. Occasionally, CDH may be asymptomatic and discovered only incidentally.\textsuperscript{67,94-97} Patients who present later in life have a much better prognosis due to milder or absent pulmonary hypoplasia and hypertension.

**TREATMENT**

**Prenatal Care**

The prenatal diagnosis of CDH has increased with the greater use of fetal ultrasound examinations. Advanced-level ultrasonography may be initiated after screening ultrasonography demonstrates discordant size and dates. A comprehensive sonographic evaluation should be made to diagnose associated anomalies (cardiovascular and neurologic) as well as signs of fetal compromise (i.e., hydrops fetalis). Once diagnosed, a karyotype should be obtained via amniocentesis or chorionic villus sampling. The mother and fetus should be referred to a tertiary perinatal center with advanced critical care capabilities such as ECMO, nitric oxide (NO) therapy, and oscillating ventilators.\textsuperscript{98} A prenatal diagnosis of CDH allows the mother and family to be properly informed of treatment options and outcomes.

Some highly selective patients may be candidates for fetal intervention. Historically, open fetal repair of CDH was attempted but with dismal outcomes.\textsuperscript{84} Based on clinical observations in infants with congenital tracheal atresia,\textsuperscript{99} fetal intervention has shifted from direct repair of the diaphragm to lung expansion techniques. A fetoscopically placed endotracheal occlusive balloon for temporary tracheal occlusion has been introduced as a therapy for the most severe cases, LHR less than 1.0, and liver herniation.\textsuperscript{100} However, the only National Institutes of Health (NIH)–sponsored, prospective, randomized trial comparing tracheal occlusion with conventional therapy did not demonstrate a survival or morbidity advantage with fetal intervention.\textsuperscript{101} However, this study did suggest that a subgroup of the most severe patients (LHR < 0.9) may still benefit from tracheal occlusion. Thus, tracheal occlusion remains of great interest as potential fetal therapy but should only be performed in the setting of a clinical trial. Currently, there is no clinical evidence that supports temporary tracheal occlusion for the treatment of prenatally diagnosed CDH.

**Resuscitation and Stabilization**

After the confirmation of the diagnosis of CDH, initial postnatal therapy is targeted at resuscitation and stabilization of the infant in cardiopulmonary distress. Management should be targeted at the physiologic sequelae of pulmonary hypoplasia and hypertension. Immediately after delivery, a rapid overall assessment is necessary to determine hemodynamic stability and severity of disease. In severe cases, prompt endotracheal intubation is warranted without high-pressure bag ventilation to avoid gastric and intestinal distention. A nasogastric tube should be introduced along with placement of arterial and venous catheters to assist in resuscitative maneuvers. Acid-base balance and oxygenation-ventilation status should be carefully monitored.

Invasive monitoring with arterial and venous catheters is important for accurate assessment of overall perfusion of the infant and estimation of the significance of pulmonary hypertension and hypoplasia. Umbilical venous catheters may be used and should be placed across the liver into the right atrium to measure central venous pressures, but this may be difficult to achieve. In addition, oxygen content and/or saturation that reflects cerebral perfusion should be available from a preductal source by either a right radial arterial catheter or a transcutaneous saturation probe.

Initial mechanical ventilation should be utilized for stabilization. High airway pressures with a peak inspiratory pressure (PIP) greater than 25 cm H\(_2\)O should be avoided to prevent iatrogenic barotrauma. Positive-pressure ventilation should maintain the preductal arterial saturation (\(\text{Sa}_2\)) above 85\% with a minimal amount of PIP. In order to maintain lower PIP, a moderate level of hypercarbia (\(\text{Pa}_2\)CO\(_2\), 45 to 60 mm Hg) is accepted without a compensatory acidosis (pH > 7.2). Occasionally, higher levels of \(\text{Pa}_2\)CO\(_2\) are tolerated.

Pulmonary hypertension and associated cardiac anomalies are evaluated with echocardiography. Clinically, pulmonary hypertension may be exhibited by differential preductal and postductal arterial saturations. However, echocardiography can better characterize the severity of disease and the degree

![Figure 24-6. This infant presented with respiratory distress and a right CDH.](image)
of pulmonary hypertension. Sonographic findings of pulmonary hypertension include poor contractility of the right ventricle, flattening of the interventricular septum, enlarged right-sided heart chambers, and tricuspid valve regurgitation. There may be right-to-left or bidirectional shunting across the ductus arteriosus.

Preductal oxygen saturations less than 85% may impair adequate tissue perfusion. In general, a preductal \( \text{PaO}_2 \) should be maintained above 60 mm Hg and a postductal \( \text{PaO}_2 \) above 40 mm Hg. Failure to provide adequate tissue oxygenation may result in metabolic acidosis, which may exacerbate the pulmonary hypertension. Pulmonary vascular resistance is increased by hypoxia and acidosis, which all should be avoided or corrected. If severe ductal shunting develops, inhaled NO can be utilized, although pulmonary hypertension in association with CDH is less responsive than other causes of pulmonary hypertension. Despite its common utilization, NO as a rescue strategy in this setting has failed to demonstrate benefit in infants with CDH.\(^{102,103}\)

Almost all infants with CDH and severe pulmonary hypertension will exhibit some left ventricular dysfunction. Vasopressor agents such as dopamine, dobutamine, and milrinone may be utilized in hemodynamically unstable patients. These inotropic agents may augment left ventricular output and increase systemic pressures to ameliorate the right-to-left ductal shunting.

**Mechanical Ventilation**

Mechanical ventilation is a critical component in the care of infants with respiratory failure secondary to CDH. The physiologic limits of the hypoplastic lung make mechanical ventilation a challenge. Hypoplastic lungs in CDH infants are characterized by a decreased number of airways and smaller airspaces. In conjunction, the pulmonary vasculature exhibits decreased vascular branching and increased adventitial and medial wall thickness.\(^ {104,105}\) This combination results in varying degrees of respiratory failure and pulmonary hypertension. Fortunately, pulmonary and vascular development continues after birth.\(^ {106,107}\)

Because of this ongoing maturation, mechanical ventilation strategies have trended to less aggressive approaches with the goal of stabilizing ventilator therapy to maintain oxygenation while limiting the risks of ventilator-induced lung injury, a major contributor to mortality.\(^ {108}\)

The type of mechanical ventilator in infants with CDH is clinician preference, but most cases of CDH can be managed using a pressure-cycled mode. The initial fraction of inspired oxygen (\( \text{FiO}_2 \)) of 1.0 is utilized to maintain adequate oxygen saturation. Typically, the utilization of higher rates and lower peak airway pressures (18 to 22 cm \( \text{H}_2\text{O} \)) while titrating the \( \text{FiO}_2 \) can maintain a preductal \( \text{PaO}_2 \) greater than 60 mm Hg or better (a preductal \( \text{SaO}_2 > 85\% \)) and a \( \text{PCO}_2 \) less than 60 mm Hg. Maintaining an acceptable \( \text{pH} \) and \( \text{PCO}_2 \) is important in managing the pulmonary hypertension.\(^ {109,110}\) The ventilation strategy of induced respiratory alkalosis by hyperventilation to reduce ductal shunting has been abandoned by most centers.\(^ {111-114}\)

Lung-protective ventilation strategies include pressure-limited ventilation rates between 30 and 60 breaths/min along with PIP less than 25 cm \( \text{H}_2\text{O} \) to minimize barotrauma.\(^ {111,115}\) Spontaneous respirations are maintained by avoiding neuromuscular paralysis and minimally set respiratory rates. This combination of spontaneous respiration and permissive hypercapnia has been a well-documented preoperative stabilization strategy with survival rates of almost 90% reported from some centers in patients with isolated CDH.\(^ {111-115}\)

If conventional ventilation fails to reverse hypercapnia and hypoxemia, high-frequency ventilation strategies may be employed. The role of high-frequency oscillatory ventilation (HFOV) in infants with CDH is based on its ability to avoid ventilatory-induced lung injury by preserving end-expiratory lung volume without overdistention. As the understanding of the CDH lungs continued to evolve, HFOV strategies also changed. Initially used in a high-pressure lung recruitment mode, this strategy demonstrated no benefit due to the nonrecruitable nature of the hypoplastic lungs.\(^ {116,117}\) High-frequency strategies as a rescue therapy for infants with profound hypoxia and refractory hypercapnia on conventional ventilators have been without much success.\(^ {118,119}\) As the concept of preoperative stabilization became better defined, HFOV began to be used as means to avoid barotrauma early in the treatment course before refractory respiratory failure, with some institutions using HFOV as primary therapy.\(^ {120-122}\) These strategies of preoperative stabilization regardless of ventilator modalities to prevent lung injury and delayed surgery have resulted in improved survival.\(^ {108,120-123}\)

To achieve lower peak airway pressures, HFOV should be maintained at a mean airway pressure less than 16 cm \( \text{H}_2\text{O} \). HFOV should be considered when PIP exceeds 25 cm \( \text{H}_2\text{O} \) with conventional therapy. The \( \text{PCO}_2 \) should be maintained in the range of 40 to 55 mm Hg by adjusting the amplitude between 35 to 45 cm \( \text{H}_2\text{O} \). Eight rib expansion of the contralateral hemithorax has been used as an initial guide to achieve optimal lung expansion without overdistention.\(^ {120,122}\)

Tidal volumes are directly related to the amplitude and inversely related to frequency. Thus, significant increases in tidal volume can be seen when frequencies are below 10 Hz. This can result in hyperinflation, which in turn may adversely affect the pulmonary vasculature, including venous return. Constant assessment of acid-base status and end-organ perfusion is necessary as lung compliance changes, or as the CDH is repaired.

**Surfactant**

Several animal studies of CDH have shown altered surfactant levels and composition.\(^ {63,124-129}\) However, human data to support this have been controversial.\(^ {65}\) Experimentally, surfactant decreases pulmonary vascular resistance, improves pulmonary blood flow, and
In addition, surfactant administration has been shown to augment NO delivery and improve gas exchange. These findings led clinicians to utilize exogenous surfactant empirically. However, clinical evidence in term and preterm infants with CDH has not shown benefit. In one study, it was suggested that surfactant therapy in term infants with CDH was associated with an increased use of ECMO, an increased incidence of chronic lung disease, and higher mortality. Similar findings were found in preterm infants despite adjusting for Apgar scores and gestational age. Even as a rescue therapy in CDH infants on ECMO, surfactant failed to demonstrate a survival advantage. Despite the lack of proven efficacy, exogenous surfactant therapy continues to be used with unknown risk and unclear benefit. Proponents of this therapy argue that the clinical evidence is based on a heterogeneous population of disease severity and that failed therapy may be due to its use in the most severe CDH infants. Given the clinical data, surfactant therapy should only be used in a randomized, controlled fashion.

Nitric Oxide

Inhaled NO is a potent pulmonary vasodilator that has been shown to have tremendous benefit in the treatment of persistent pulmonary hypertension of the neonate (PPHN). In clinical studies, NO improved oxygenation and decreased the need for ECMO in infants with respiratory failure secondary to PPHN. However, the efficacy of NO for pulmonary hypertension secondary to CDH has not been as well supported. The need for ECMO or a reduction in mortality has not been shown with NO use in CDH infants. In the Neonatal Inhaled Nitric Oxide Study Group trial, the CDH subgroup had a greater likelihood for ECMO or death. The response to NO is variable and unpredictable in infants with CDH. Some may demonstrate a rebound pulmonary hypertension that is more difficult to control than the initial disease. Furthermore, the effect appears to be transient and does not prevent progression toward ECMO use. Thus, the role of inhaled NO has not been clearly defined and should not be routinely used. NO should be reserved for infants who persistently demonstrate suprasystemic pulmonary pressures in the setting of optimized pulmonary and cardiac function to reduce right ventricular pressures.

Other pulmonary vasodilator agents have been utilized in the treatment of pulmonary hypertension in infants with CDH. Sildenafil is a 5-phosphodiesterase (5-PDE) inhibitor that has been utilized as a transitional medication to wean off NO for unresolving pulmonary hypertension. Widely used for PPHN and pulmonary hypertension secondary to congenital heart disease, sildenafil can be used in both oral or intravenous forms. Epoprostenol (intravenous prostacyclin) and bosantan (a nonspecific endothelin-1 receptor inhibitor) have all been used in infants with CDH but the experience to date is limited.

Extracorporeal Membrane Oxygenation

ECMO for infants with CDH was first introduced as a potential therapy for infants who likely had severe ventilator-associated lung injury. Since then, ECMO strategies have evolved as understanding of CDH with its associated pulmonary hypoplasia and hypertension has improved. CDH accounts for approximately one fourth of all infants requiring ECMO for respiratory failure. Almost 30% of CDH infants will receive ECMO during their hospital course. Prior to the era of preoperative stabilization, ECMO was associated with only a modest improvement in survival in high-risk CDH infants.

Initially, strict criteria were established as indications for ECMO use in CDH. These included an oxygenation index greater than 40 and persistent alveolar-arterial gradient greater than 610 mm Hg. Today, those criteria have been softened and the most common indication for ECMO is a “failure to respond” to therapy. In efforts to maintain lung-protective ventilation, clinicians have opted for ECMO rather than escalation of positive airway pressures. Relative contraindications include significant congenital anomalies, lethal chromosomal anomalies, intracranial hemorrhage, and gestational age less than 34 weeks. Ideally, ECMO candidates should have a birth weight greater than 2 kg owing to increased risk of intracranial hemorrhage, but some have reported benefit in infants weighing less than 2 kg.

ECMO was initially utilized as a postoperative rescue therapy, but its role has evolved. In combination with other adjunctive modalities such as HFOV, ECMO is now routinely used as a component of preoperative stabilization. The strategy of stabilization with ECMO and delay in surgery has been shown to be beneficial, with a reported survival of 67% in high-risk patients. These findings were further supported by the CDH study group that reported 85% of infants had ECMO before repair. Of those, 54% were repaired while still on ECMO and 29% repaired after ECMO with 16% never making it to repair. Infants who underwent repair while on ECMO had a 50% mortality, compared with 17% after ECMO.

The optimal timing of CDH repair is controversial and surgeon dependent. With more repairs of CDH on ECMO, bleeding became an increasingly recognized complication. The introduction of aminoacaproic acid, a fibrinolysis inhibitor, has significantly decreased bleeding complications. Bleeding may also be reduced with early repair on ECMO before the development of coagulopathy and significant edema. Some surgeons have recommended repair when pulmonary hypertension has resolved but prior to decannulation. This allows reinstitution of ECMO if respiratory failure and/or pulmonary hypertension recurs. Others have requested that infants be decannulated and on conventional ventilation before repair. Although rare, recurrent pulmonary hypertension can occur after surgery, requiring a second run of ECMO. Survival for second-run ECMO patients is approximately 50%.
Today, ECMO is routinely used to stabilize patients before operation. Although results are dependent on patient selection and entry criteria, survival has been reported between 60% and 90%. \(^{98,111,146,161,162}\) Without ECMO, the predicted mortality in the high-risk cohort reaches 80%. \(^{146}\) Despite these data, ECMO for CDH is not universally accepted. Some authors report no survival advantage with ECMO.\(^{163,164}\) Others cite an increased neurologic complication rate with ECMO use in CDH infants compared with other indications such as PPHN.\(^{165,166}\) Some institutions report an 80% survival of infants with CDH without use of ECMO.\(^{167,168}\) Nonetheless, in most centers ECMO remains a component in the armamentarium for treating CDH infants with refractory cardiopulmonary failure.

**Surgery**

The surgical approach to the repair of CDH has changed dramatically in the past 25 years. Historically, neonates with CDH were brought to the operating room almost immediately after birth to emergently relieve the compressed lung by reducing the intra-abdominal contents from the chest. Often, this maneuver was followed by a transient period of cardiopulmonary stability or improvement.\(^{169,170}\) However, frequently, the infant would develop progressive respiratory failure, elevated pulmonary vascular pressures, right-to-left ductal shunting, unrecoverable hypoxemia, and eventually death. With improved understanding of the pathophysiology of CDH, repair of CDH is no longer considered a surgical emergency. Nonetheless, timing of the surgical repair of the diaphragm remains controversial.

The shift toward a delay in surgery after preoperative stabilization occurred after evidence was introduced that pulmonary compliance was actually worse after repair.\(^ {171}\) Several factors have been implicated, including increased intra-abdominal pressure and distortion of the repaired diaphragm. In addition, surgical repair has not been shown to improve gas exchange. Several studies have evaluated early versus delayed repair of CDH without demonstrating a difference in mortality or need for ECMO.\(^ {172-174}\) These include two randomized trials of early (<12 hours) versus delayed repair after 24 hours\(^ {174}\) and after 96 hours.\(^ {172}\) Since the adoption of the delayed repair strategy, several centers have reported improved survival rates.\(^ {111,174-177}\) Although modifications of surgical techniques and timing have contributed to this improvement, concomitant advances in neonatal critical care as well as a better understanding of the disease and outcomes have been the greater contributors to decreased mortality. Importantly, there has been no clinical evidence that specifically attributes a delay in surgery to improved outcomes over immediate repair.\(^ {178}\)

Timing of operation remains with clinical judgment and surgeon discretion. Some clinicians will opt for repair once the respiratory failure has stabilized (low peak airway pressures and inspired oxygen requirements) and after echocardiography demonstrates a resolution or stability of the pulmonary hypertension. This typically occurs 24 to 48 hours after clinical evidence of ductal shunting has resolved. Although CDH can be repaired on HFOV, most surgeons will wait until the infant is transitioned to a conventional mechanical ventilator.

The repair of a CDH may be as variable as the clinical management. A subcostal incision on the ipsilateral side of the hernia is the traditional approach. Less than 10% of surgeons prefer a thoracic approach.\(^ {177}\) The intra-abdominal contents should be reduced out of the thorax with careful attention to the spleen, which can be caught and torn on the rudimentary rim of diaphragm. A true hernia sac, which is only present less than 20% of the time, should be identified and excised.\(^ {180}\) The thoracic and abdominal cavities should be inspected for associated pulmonary sequestrations. The extent of the diaphragmatic hernia should be examined and assessed.

The type of repair is dependent on the size of the diaphragmatic defect. If the defect is small, a tension-free primary closure should be performed with nonabsorbable sutures with or without pledgets. If the defect is large, attempted primary closure may cause significant tension or flattening of the diaphragm, resulting in decreased pulmonary compliance. Alternatively, a diaphragmatic replacement may be employed to restore a tension-free, diaphragmatic shape (Fig. 24-7). Several types of prosthetic and biosynthetic patch materials have been utilized. Traditionally, a polytetrafluoroethylene (PTFE or Gore-Tex, W. L. Gore, Newark, DE) patch has been used.\(^ {179}\) With the use of a 1-mm thickness patch, the prosthesis is cut slightly larger than the diaphragmatic defect and is sewn to the residual diaphragm or surrounding tissue with nonabsorbable suture. The disadvantage of prosthetic material is the lack of material growth, resulting in a significant recurrence rate of nearly 50%.\(^ {181}\) To prevent this, the patch is tailored in a “cone shape” that may resemble the native diaphragm. This technique has demonstrated a reduction in recurrence rate from 26% to 9%.\(^ {182}\) Large defects with an adequate

![Figure 24-7](image-url)
posterior rim of diaphragm may require suturing the patch to the abdominal wall or encircling the ribs for adequate fixation.

Outcomes regarding the type of prosthetic patch material are mixed. Opponents of prosthetic patch material, such as PTFE, cite an unacceptable recurrence rate, chest wall deformity, and intra-abdominal complications, such as small bowel obstruction. With a recurrence rate as high as 50%, alternative biosynthetic materials have been introduced to repair CDH. Currently, the most popular material is small intestine submucosa (Surgisis or SIS, Cook, Inc., Bloomington, IN) or human acellular dermal matrix (Alloderm, LifeCell, Branchburg, NJ). These bioactive patches may serve as a matrix for permanent tissue ingrowth. Some institutions have adopted bioactive materials as the primary patch for repair of large diaphragmatic hernias. Proponents of biosynthetic patches claim the patch material is less adherent to small bowel and allows for tissue engraftment that grows with the patient. However, the largest series comparing SIS to Gore-Tex demonstrated similar recurrence rates and no difference in small bowel obstruction. Long-term outcomes with biosynthetic patches for CDH remain to be seen. Certainly, the type of CDH patch material needs to be studied in a prospective fashion.

Recurrences after CDH repairs have prompted investigation into alternatives to prosthetic and biosynthetic materials. Some surgeons have utilized muscle flaps for primary and recurrence repairs. In small case series, an abdominal wall muscle flap using internal oblique and transversalis abdominal muscles has been described to cover very large primary or recurrent diaphragmatic defects. Thoracic wall musculature has also been widely utilized. Latissimus dorsi and serratus anterior muscles have been described with isolated success.

Local advancement with a reversed latissimus dorsi flap with microneural anastomosis of the thoracodorsal nerve to the phrenic nerve has been described for recurrent herniations. With this technique, the neodiaphragm was able to demonstrate nonparadoxic motion by fluoroscopy and ultrasonography. Muscle flaps may be advantageous in very large defects and in diaphragmatic agenesis.

Postoperative tube thoracostomy is not necessary and probably not indicated. An exception may be CDH repair on ECMO because bleeding complications should be expected. The thoracic space will eventually fill with air and fluid, the lung will gradually grow, and the rib spaces may narrow to decrease the overall thoracic cavity. Tube thoracostomy is used only for postoperative chylothorax or accumulation of pleural fluid causing hemodynamic compromise. If a chest tube is warranted, the tube is placed in the thoracic cavity before final closure of the diaphragm. Chest tubes should be placed to water seal rather than suction. Aggressive negative pressure can shift the mediastinum to the ipsilateral hemithorax creating overdistention of the contralateral lung. Symptomatic pleural fluid may be treated with repeated thoracentesis. If used, chest tubes should be removed early to avoid infection.

If the CDH is repaired via laparotomy, the abdominal domain may not be able to accommodate the reduction of the intestinal contents. Closure of the abdominal wall may result in an abdominal compartment syndrome. A “tight abdomen” may cause respiratory compromise in an already tenuous infant. Careful attention should be paid to the peak airway pressures as the abdominal fascia is closed. Respiratory compromise should prompt the abdomen to be left open. This scenario is more often seen with CDH infants on ECMO. Temporary closure can be achieved with skin, prosthetic silo, or abdominoplasty. Delayed closure, especially in those infants on ECMO, should be attempted after the general edema has resolved or the intra-abdominal domain has enlarged.

Special operative considerations should be made for CDH infants on ECMO. In addition to the abdominal compartment issues, hemorrhagic complications are more likely due to the anticoagulation required for ECMO. Fibrin or thrombin sealants should be liberally used to reduce suture line hemorrhage. Aminocaproic acid should be given before operation and for 2 to 3 days postoperatively to prevent bleeding complications.

The therapeutic goals of postoperative ventilation should be similar to the preoperative goals, that is, to minimize barotrauma. Infants may experience a transient period of cardiopulmonary improvement that may allow clinicians to wean ventilatory support. However, rapid decreases in FiO₂ should be avoided to prevent triggering pulmonary vasospasm and recurrent pulmonary hypertension.

Advances in minimally invasive techniques have led to an increase in thoracoscopic and laparoscopic repairs of CDH (Fig. 24-8). Concerns regarding the minimally

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Figure 24-8.  A, Laparoscopic view of a left-sided CDH in a 2-week-old with respiratory distress. The bowel and spleen have been reduced. The edges of the diaphragmatic defect are well seen (arrows). A very thin sac was present. B, The sac was removed and a primary closure was possible.
invasive approaches have centered around prolonged operations precipitating respiratory complications, triggering or exacerbating pulmonary hypertension, and resulting in an unnecessary increase in mortality. With careful patient selection, minimally invasive repairs have been successfully performed, both laparoscopically and thoracoscopically.¹⁹⁷-¹⁹⁹ This approach has been utilized with primary repair as well as prosthetic patch closure of the CDH.²⁰⁰ Laparoscopic and thoracoscopic operations are feasible without a demonstrable advantage to either. However, patient selection remains the main determinant of success. A preoperative patient selection criteria for thoracoscopic repair of CDH has been proposed.¹⁹⁹ Preoperative requirements included minimal ventilatory support (PIP < 24 mm Hg), no clinical or sonographic evidence of pulmonary hypertension, and an intra-abdominal stomach. In a small series of seven patients, results were similar to open CDH repairs. The long-term outcomes with minimally invasive approaches to CDH remain to be seen. Thus, long-term follow-up outcomes are not available. Nonetheless, large international registries such as the CDHR offer some advantages. The CDHR is a vehicle to collect data from a large number of patients. The CDHR reflects changes in management and outcomes over time. Finally, individual institutions can compare their risk-adjusted outcomes to other institutions as a method of quality assurance.

**Survival**

As with all outcomes studies regarding CDH, survival analysis remains difficult to interpret due to the tremendous variations in patient disease, management strategies, and operative techniques. Unique to individual institutions are differences in ventilation strategies, availability and entry criteria for ECMO, and operative timing. One method to achieve better comparisons of outcomes is the development of risk stratification of patient disease. In 2001, the CDHSG published the first attempt at predicting outcome based on risk stratification.²⁰¹ The study examined 1054 infants with CDH by applying a risk assessment tool created by a logistical equation. Patients were categorized into low-, moderate-, and high-risk groups, which correlated with actual mortality. Overall survival was 64% in which birth weight and 5-minute Apgar scores had the strongest correlation. Survival rates for CDH among institutions are highly variable even when risk adjusted. Although the overall survival of liveborn infants has been reported around 60%, individual centers have varied from 25% to 83%.⁹ This variation may be a reflection of the increasing prenatal diagnosis of CDH in which the most severe cases are transferred to tertiary care centers.

**Pulmonary Outcomes**

For many infants who survive the neonatal period with CDH, pulmonary function is excellent. Prior to the era of ECMO and lung-protective ventilation, long-term survivors were routinely reported as healthy children without respiratory disease.⁵³,²⁰²-²⁰⁴ However, with improved survival, more severe CDH infants are available for follow-up. Children with a history of CDH have demonstrated both functional and radiographic evidence of chronic lung disease. Pulmonary function has been reported to be normal in 50% to 70% of CDH survivors.⁵³,²⁰²,²⁰⁵,²⁰⁶ The remainder exhibit some form of restrictive or obstructive respiratory symptoms. Approximately 25% of children beyond the age of 5 years have demonstrable signs of obstructive airway disease. One hundred consecutive CDH survivors were recently evaluated. ECMO and the need for patch repair were independent predictors of pulmonary outcome.²⁰⁶ The use of ECMO significantly correlated with diuretic dependence at the time of discharge.⁸¹ While only 16% required oxygen at discharge, 53% required at least transient usage of bronchodilators within the first year. Similarly, 41% were either dependent on or intermittently needing corticosteroids during the first year. Others have demonstrated similar pulmonary morbidities. In another

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**OUTCOMES**

Clinical outcomes in regard to the treatment and management of infants with CDH have traditionally been difficult to interpret. Because the estimated incidence of CDH is low (1 in 2500 to 4000 live births), it has become evident that single institutions, regardless of their volume, would have difficulty in generating meaningful, evidence-based outcomes.⁹,¹⁰ In addition, patient characteristics and clinical practices are very different and each institution’s ability to offer state-of-the-art neonatal critical care is highly variable. Furthermore, data from a very heterogeneous disease population, such as CDH, are often pooled to generate single reports.

**Congenital Diaphragmatic Hernia Registry (CDHR)**

The Congenital Diaphragmatic Hernia Study Group (CDHSG) was established in 1995 as an international group of clinicians and researchers interested in developing a registry of all infants born with CDH. The CDHSG recognized the limitations of individual institutions in producing meaningful data on their own. As an observational database, the CDHR was created by a network of voluntary centers to ask specific clinical questions, recommend specific therapy as needed, and monitor outcomes of various management and treatment strategies. Since 1995, more than 90 centers from 10 countries have submitted data on more than 4000 infants with CDH. Participation among centers has varied, but currently there are over 50 active centers in the CDHSG with an average total submission of 340 infants per year.¹

Data from the CDHR must be used with caution as with all outcome studies of CDH. There is a wide spectrum of patients within institutions and a wide spectrum of institutions within the CDHSG. Patients are only followed until hospital discharge or death.
study, chronic lung disease was found in 22% of surviving infants with CDH with a 2-year follow-up.\textsuperscript{207} As with previous studies, ECMO and patch repair were the dominant factors of poor outcomes.

Respiratory infections appear to have a higher prevalence in children with CDH.\textsuperscript{107,202,208-210} Viral bronchiolitis, such as respiratory syncytial virus (RSV), is the most common pathogen seen in children younger than 3 years of age, suggesting a need for RSV prophylaxis.\textsuperscript{206} Recurrent pneumonias have been reported in 26% to 39% of CDH survivors with at least 10 years of follow-up.\textsuperscript{107,209}

Obstructive pulmonary disease is commonly reported in children with CDH. Asthma and general symptoms of bronchospasm and wheezing are well documented.\textsuperscript{155,210,211} Although the severity of these symptoms appear to improve with age, most children will still exhibit some combination of obstructive and restrictive pulmonary function and are more reactive to pharmacologic agents.\textsuperscript{210-213} After correcting for lung size, lower functional volumes and not primary obstruction of the airways were the cause of abnormal pulmonary function tests in one study.\textsuperscript{211}

Although lung development begins early in gestation, alveolar and pulmonary vascular maturation continue well after birth. In CDH, lung hypoplasia will affect both lungs with a reduction in airway and pulmonary artery divisions. As demonstrated in ventilation/perfusion ($V/Q$) radionuclide scans, pulmonary hypoplasia will persist despite continued lung growth.\textsuperscript{211,212,214} V/Q mismatches are predominantly due to abnormal lung perfusion. Follow-up V/Q scans have demonstrated an increase in lung volume but not in lung perfusion. Because the pulmonary vasculature and alveoli grow concurrently, normalization or improvement in pulmonary function must be due to increased lung volume. This is further supported by increased alveolar size after neonatal repair of CDH.\textsuperscript{215,216} Although V/Q scans in children with CDH have provided valuable information, their predictive value for chronic lung disease in CDH survivors remains to be determined. In a review of 137 CDH infants, 61% had V/Q mismatching at the time of their last scan. Patch repair and ECMO again had the strongest association, but definitive causation could not be established.\textsuperscript{217}

Chest radiographs (CXR) are routinely abnormal and consistently demonstrate evidence of bronchopulmonary dysplasia.\textsuperscript{202,206,213,218} Common features of chronic lung disease include hyperlucency, hyperinflation, persistent lung hypoplasia, decreased pulmonary vasculature, unknown opacities, persistent mediastinal shifts, and a chronic abnormal diaphragm position. In general, plain radiographs have no correlation with clinical symptoms in CDH with the exception of recurrent hernias. Approximately one third of CDH children will have an abnormal chest film.\textsuperscript{213}

**Neurologic Outcomes**

As more infants with CDH are surviving, multidisciplinary follow-up has become as important as the in-hospital care. Although most patients may resolve their pulmonary or gastrointestinal issues, neurodevelopmental morbidities may be harder to detect. The lack of close follow-up and adequate simple tools to measure neurodevelopment may lead to undetected morbidity. Thus, close monitoring of neurodevelopment is imperative. Continued motor and language problems, even at 3 years of age, have been found.\textsuperscript{219}

A significant percentage of CDH survivors will have neurodevelopmental sequelae, including developmental delay, motor and cognitive disabilities, and behavior disorder.\textsuperscript{165,166,220-222} Several factors have been attributed to these outcomes, including ECMO use, disease severity with prolonged hypoxia, and prolonged hospitalizations. However, confounding evidence has made deciphering the root cause of neurodevelopmental sequelae from CDH difficult. In 1995, one study evaluated 82 CDH children at 1 year who had required ECMO use.\textsuperscript{220} Developmental delay was significantly more prevalent when compared with children in whom ECMO was used for other indications. Another study demonstrated associated abnormal neuroimaging in children with neurodevelopmental delays in ECMO survivors of CDH.\textsuperscript{165} However, other studies with large patient groups have not implicated ECMO. Stolar and colleagues reported on 51 ECMO survivors and concluded that ECMO was not a risk factor for neurologic deficits.\textsuperscript{166} Another study found no differences in neurologic outcomes in 130 children who underwent ECMO for CDH compared with other diseases.\textsuperscript{207} Other factors such as low socioeconomic status and prematurity have also been suggested as contributors.\textsuperscript{166,221-223}

Sensorineural hearing loss (SNHL) is a common neurologic sequel of CDH. The prevalence of SNHL ranges from none in some series to 100% in others.\textsuperscript{207,224} The etiology of SNHL remains difficult to decipher. SNHL is seen in patients with and without ECMO.\textsuperscript{224,226} Several ototoxic medications are routinely used in the acute and chronic care of infants with CDH, such as diuretics, antibiotics, and muscle relaxants.\textsuperscript{225} Even mechanical ventilation has been linked to SNHL.\textsuperscript{228} Most likely, it is a combination of treatment and severity of disease. Stringent audiologic testing is warranted because SNHL may cause speech delays and further impair other aspects of neurodevelopment.

**Gastrointestinal Outcomes**

Gastroesophageal reflux disease (GERD) is a common gastrointestinal sequela of CDH. The cumulative incidence has been reported to be 40% of all CDH survivors. Approximately half require surgical intervention,\textsuperscript{229} although individual centers have reported higher percentages.\textsuperscript{230,231} The incidence among institutions is variable, depending on the mode of diagnosis: clinical symptoms, upper gastrointestinal contrast radiographs, pH monitoring, or impedance plethysmography. Although GERD can be self-limiting, several studies have reported long-term symptoms. One study reported that 63% of patients required GERD medications after 2 years.\textsuperscript{232} Another report found a
similar percentage (63%) in a long-term follow-up of 29 years. A final study noted that 50% had symptomatic GERD after 1 year of age.

Despite its high prevalence, the etiology of GERD in association with CDH is unclear. Certainly, anatomic changes with CDH may contribute to GERD. Esophageal ectasia may occur due to abnormal fetal development secondary to mediastinal shift, resulting in an abnormal lower esophageal sphincter. The presence of an intrathoracic stomach due to herniation may cause the maldevelopment of the gastroesophageal junction. The side of the CDH may cause a differential growth pattern and subsequent shortening of an intra-abdominal esophagus. Distortion of the esophageal hiatus and increased intra-abdominal pressure from reduction of the viscera have also been implicated as postsurgical causes of GERD. Owing to the frequency of symptomatic GERD, primary antireflux surgery has been recommended by some surgeons, especially for large defects.

A significant number of CDH survivors demonstrate evidence of failure to thrive. Many fall well below the 25th percentile in weight despite adequate caloric intake and aggressive feeding management (i.e., via gastrostomy). Symptomatic GERD may be a contributor, but an underestimation of the caloric needs may be the more significant reason. Survivors of CDH may have an increased metabolic demand due to chronic lung disease, resulting in increased respiratory work. These factors, in addition to oral aversion due to prolonged hospitalization, result in nutritional demands that may be underappreciated.

Gastrointestinal surgical issues are commonly seen in CDH children. Adhesive intestinal obstruction, intestinal ischemia, volvulus secondary to malrotation, and intestinal perforation are well documented. Intestinal obstruction occurs in up to 25% of patients. Postoperative adhesions due to repair of the diaphragm or antireflux surgery have been reported, with the use of prosthetic patch material as a significant factor. Other causes include malrotation, intestinal dysmotility, and recurrent hernia with incarceration. Recurrent CDH occurs in approximately 50% of patients within 3 years and is most commonly associated with a large defect size and subsequent use of prosthetic patch material. Patients who underwent ECMO appear to have the highest risk of recurrence. This is most likely due to the patients having the most severe disease secondary to the largest defects with the subsequent need for prosthetic patch repair.

Musculoskeletal Outcomes

The relationship between musculoskeletal development and CDH is evidenced by the frequency of chest wall deformities seen in children with CDH. The estimated incidence is between 21% and 48%. Pectus deformities, chest asymmetry, and scoliosis are the most common. Scoliosis may be severe and continue to progress until adulthood. Some authors have suggested that the reason for progression is due to tension on the diaphragm, thoracotomies without muscle-sparing techniques, or a small hemithorax due to hypoplastic lungs. Most patients are asymptomatic and do not require surgical intervention.

Follow-up Guidelines

Critically ill infants with CDH often require prolonged and intensive therapies such as ECMO during hospitalization. These result in long-term sequelae that require medical attention after discharge. Pulmonary, neurologic, gastrointestinal, and musculoskeletal complications necessitate a multidisciplinary team of surgical, medical, and developmental specialists. In 2008, the Section on Surgery and Committee on Fetus and Newborn for the American Academy of Pediatrics established a series of guidelines for the follow-up care of infants with CDH. These recommendations begin before discharge and extend through age 16 years. The guidelines include a formal follow-up plan to facilitate the early recognition of co-morbidities (Table 24-1).

NOVEL INTERVENTIONS

Even with advances in neonatal critical care, the treatment of infants with CDH remains a challenge to pediatric surgeons, neonatologists, and intensivists. Despite increased survival rates in the past 25 years, many infants with CDH die or develop debilitating morbidities. Thus, researchers continue to investigate novel therapies for infants with CDH.

Fetal Intervention

The impetus for fetal therapy for CDH coincided with the advances in prenatal diagnosis. Improvements in fetal ultrasonography revealed the true natural history of CDH and the hidden mortality during gestation and soon after birth. These poor outcomes prompted the researchers at the University of California, San Francisco, to explore fetal surgery for CDH. Subsequently, fetal CDH intervention evolved from open fetal surgery to the current state of endoscopic endoluminal tracheal occlusion.

The prerequisite for any fetal intervention is the ability to accurately diagnose CDH and predict severity of disease and survival. The most widely accepted prenatal sonographic prognosticators have been liver herniation and LHR, which have been discussed previously. Liver herniation and an LHR less than 1.0 are recognized as fetal characteristics that portend the poorest outcomes.

After years of unfavorable outcomes with open fetal repair of CDH, prenatal intervention evolved to tracheal occlusion. Based on clinical observations that tracheal atresia causes pulmonary hyperplasia, novel animal experiments of lung distention, and an improved understanding of fetal lung growth, therapeutic tracheal occlusion was introduced as a treatment for pulmonary hypoplasia secondary to CDH. Current techniques involve endoscopic placement of an occlusive balloon without
Table 24-1  Recommended Schedule of Follow-up for Infants with CDH

<table>
<thead>
<tr>
<th>Before Discharge</th>
<th>1-3 mo after Birth</th>
<th>4-6 mo after Birth</th>
<th>9-12 mo after Birth</th>
<th>15-18 mo after Birth</th>
<th>Annual through 16 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, length, occipital-frONTAL circumference</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>X</td>
<td>If patched</td>
<td>If patched</td>
<td>If patched</td>
<td>If patched</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
<td>Per childhood guidelines</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Childhood immunizations</td>
<td>RSV season during first 2 years after birth (if evidence of chronic lung disease)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>RSV prophylaxis</td>
<td>X</td>
<td>If previously abnormal or if on supplemental oxygen</td>
<td>X</td>
<td>If previously abnormal or if on supplemental oxygen</td>
<td>X</td>
</tr>
<tr>
<td>Echocardiogram and cardiology follow-up</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Head CT or MRI</td>
<td>If (1) abnormal finding on head ultrasound examination; (2) seizures/abnormal neurologic findings; or (3) ECMO or patch repair</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hearing evaluation</td>
<td>Auditory brain-stem evoked response or otoacoustic emissions screen</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Developmental screening evaluation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Neurodevelopmental evaluation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Oral aversion screening</td>
<td>X</td>
<td>X</td>
<td>If oral feeding problems</td>
<td>If oral feeding problems</td>
<td>If oral feeding problems</td>
</tr>
<tr>
<td>Upper gastrointestinal study, pH probe, and/or gastric scintiscan</td>
<td>Consider for all patients</td>
<td>If symptoms</td>
<td>If symptoms</td>
<td>Consider for all patients</td>
<td>If symptoms</td>
</tr>
<tr>
<td>Esophagoscopy</td>
<td>If symptoms</td>
<td>If symptoms</td>
<td>If symptoms or if abnormal gastrointestinal evaluations</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Scoliosis and chest wall deformity screening (physical examination, chest radiograph, and/or CT of the chest)</td>
<td>If symptoms</td>
<td>If symptoms</td>
<td>If symptoms</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

RSV, respiratory syncytial virus; ECMO, extracorporeal membrane oxygenation.
maternal laparotomy or general anesthesia. Tracheal balloons are placed between 24 and 28 weeks’ gestation and deflated at 34 weeks. This strategy of temporary tracheal occlusion is based on avoiding the need for an ex-utero intrapartum treatment (EXIT) procedure at delivery. In addition, prolonged tracheal occlusion has been demonstrated to differentiate type II pneumocytes into type I pneumocytes, resulting in surfactant deficiency and necessitating the need for balloon removal.

An NIH-sponsored randomized trial comparing fetal tracheal occlusion versus standard postnatal care was reported in 2003. After 24 cases (11 by tracheal occlusion), the study was terminated early due to comparable survival outcomes (77% by postnatal care, 73% by tracheal occlusion) during interim analysis. The hazard ratio for mortality associated with tracheal occlusion, as compared with conventional therapy, was 1.2 (95% confidence interval [CI]: 0.29 to 4.67). However, when stratified based on LHR, survival was significantly better for LHR greater than 0.9. In fact, the hazard ratio for death with tracheal occlusion was 0.13 (95% CI: 0.03 to 0.64). This study recognized the wide spectrum of disease based on LHR and speculated that the patients with the most severe disease may still benefit from tracheal occlusion. Despite these results from the randomized trial, tracheal occlusion continues to be investigated owing to the significant mortality of infants with LHR less than 1.0 and liver herniation.

The FETO ( Fetoscopic Tracheal Occlusion ) task group, a European perinatology organization, created a multicenter prospective observational study. In an attempt to select a more severe subset based on data from the NIH trial, the study included fetuses with liver herniation and LHR less than 1.0. In the initial 21 patients (15 left-sided CDH and 6 right-sided CDH), the investigators reported a survival of 48% for tracheal occlusion compared with 8% in the nonocclusion group. In addition to the survival advantage, the study also demonstrated an improvement in perinatal complications such as prematurity and premature rupture of membranes. The latest series reported overall survival of 57% for tracheal occlusion with survival greater than 62% for LHR between 0.6 and 1.0. Although impressive, these results warrant further investigation in that the survival for LHR of 0.8 to 0.9 (78%) was higher than survival for LHR greater than 1.0 treated postnatally (65%). Furthermore, study limitations have prevented the widespread adoption of tracheal occlusion based on the European data. Control cases were taken from multiple centers that could not provide a standardized postnatal approach or reflect recent advances in postnatal care.

Long-term outcome with morbidity has yet to be reported for tracheal occlusion. However, one study examined pulmonary function in 20 patients (9 with conventional therapy and 11 with tracheal occlusions) from the NIH-sponsored randomized trial. Infants were evaluated during the first 24 hours of life, before and after operative repair, and before elective extubation. The study demonstrated slight improvements in respiratory compliance and alveolar-arterial oxygenation gradients in patients who had undergone tracheal occlusion. However, other long-term outcomes remain to be seen. Based on the only randomized clinical trial, there appears to be no significant benefit from tracheal occlusion for the treatment of CDH. Although proponents of fetal intervention suggest that a subgroup of the most severe patients (liver herniation and LHR < 0.9) may still benefit from fetal intervention, the true efficacy of fetal tracheal occlusion for these severely affected infants will require a prospective randomized trial before its universal acceptance.

Prenatal Glucocorticoids

The hypoplastic lungs of CDH infants are structurally and functionally immature. Biochemical markers for lung maturity demonstrate decreased total lung DNA, total lung protein, and desaturated phosphatidylcholine in addition to deficiency of surfactant. In animal models of CDH, prenatal administration of glucocorticoids has demonstrated a reduction in alveolar septal thickness, increased DNA synthesis, and increased total lung protein production. Thus, antenatal administration of glucocorticoids has been used to improve lung function. Initial results from small patient studies seemed promising. However, a prospective randomized trial conducted by the CDHSG failed to demonstrate any benefit to antenatal corticosteroid therapy for CDH. In the multicenter trial, mothers received three weekly administrations of prenatal betamethasone. The study, which included 32 patients (15 on placebo and 17 on steroids), failed to show a difference in overall survival benefit, length of mechanical ventilation, length of hospitalization, or need for supplemental oxygen at 30 days. The study compared its results with a large cohort from the CDHR with comparable outcomes.

ANTERIOR HERNIAS OF MORGAGNI

Anterior diaphragmatic hernias of Morgagni account for less than 2% of all congenital diaphragmatic hernias. The foramen of Morgagni hernia results from the failure of the crural and sternal portions of the diaphragm to fuse. This can occur on either side at the junction of the septum transversum and thoracic wall where the superior epigastric artery (internal mammary artery, intrathoracically) traverses the diaphragm. Approximately 90% of unilateral hernias occur on the right. Only 7% occur bilaterally. Operatively, these may communicate in the midline and appear as a very large anterior hernia. Typically, a hernia sac is present with herniation of omentum, small intestine, and/or large intestine but may also contain liver and spleen. Malrotation may also be found. The majority of children with Morgagni hernia are asymptomatic and thus are rarely diagnosed during the neonatal period. When these hernias become symptomatic, pulmonary symptoms are usually not
the primary complaint. Children may have general epigastric discomfort such as vomiting and coughing due to intermittent obstruction.\textsuperscript{255,257} Acute cases may present as intestinal ischemia with necrosis and perforation as well as gastric volvulus.\textsuperscript{258,259} Herniation into the pericardium causing tamponade has been reported.\textsuperscript{260}

Chest radiographs of Morgagni hernias may exhibit a well-defined air-fluid level in the midline of the chest. A lateral chest radiograph will demonstrate the hernia in the retrosternal space (Fig. 24-9). Small hernias may require a contrast radiograph or CT scan to confirm the diagnosis. Because of the risk of incarceration and strangulation, these hernias should be repaired relatively soon after diagnosis. Operative repair usually entails reduction of herniated viscera, excision of the hernia sac, and closure of the diaphragm to the posterior rectus sheath at the costal margin. Open procedures can be performed through an upper transabdominal incision. Laparoscopic techniques have been well documented (Fig. 24-10).\textsuperscript{261,262} Although most defects can be repaired primarily, large defects may require patch repairs. The use of PTFE and biosynthetic (Surgisis, Cook Inc., Bloomington IN) patches has been described.\textsuperscript{197,263} The long-term outcome regarding recurrence is yet to be defined.

An anterior diaphragmatic hernia may be found in association with a pentalogy of Cantrell due to a failure in the development of the septum transversum.\textsuperscript{264} Pentalogy of Cantrell is a rare cluster of congenital anomalies that include omphalocele, cardiac defects, ectopic cordis, and an anterior diaphragmatic defect extending into the pericardium. The cardiac defect is the most severe problem and is the main cause of mortality.

**DIAPHRAGMATIC EVENTRATION**

Eventration is the abnormal elevation of the diaphragm resulting in a paradoxical motion during respiration that interferes with proper pulmonary mechanics and function.\textsuperscript{265,266} Congenital eventration results from the incomplete development of the central tendon or muscular portion of the diaphragm. Most commonly left sided, bilateral congenital eventration has been reported.\textsuperscript{267} The muscle is typically present but does not move in a coordinated fashion. The diaphragm is

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**Figure 24-9.** A, Chest radiograph in a neonate with a retrosternal hernia. Anteroposterior film demonstrates air-filled loops of bowel above the diaphragm and posterior to the sternum (arrow). B, Lateral projection confirms the retrosternal position of the herniated viscera (arrow).

**Figure 24-10.** Laparoscopic view of a Morgagni hernia. This anterior hernia (white arrow) is to the left of the falciform ligament (asterisk) with a deep sac that was excised. The large bowel (dotted arrow) was reduced from the hernia defect, and the defect was closed with a biosynthetic patch. (From Holcomb GW III, Ostlie DJ, Miller KA: Laparoscopic patch repair of diaphragmatic hernias with Surgisis. J Pediatr Surg 40:e1-e5, 2005.)
thin, which may be indistinguishable from a hernia sac in CDH. Large eventrations may interfere with lung development due to the paradoxical motion, and the elevated diaphragm may decrease the thoracic space. Similar to CDH, congenital eventration can result in lung hypoplasia, although this is uncommon. Persistent fetal circulation and pulmonary hypertension are usually not seen with eventration. Diaphragmatic eventration may also be acquired due to paralysis of the phrenic nerve. This can occur secondary to mediastinal tumors, congenital heart surgery, or birth trauma. The incidence after congenital cardiac surgery has been reported to be approximately 5%, with the highest incidence after Fontan and Blalock-Taussig shunt procedures. Diaphragmatic eventration may be asymptomatic but typically presents acutely as respiratory distress and tachypnea in the newborn or more indolently with recurrent respiratory infections and wheezing. Neonates may have feeding intolerance due to disordered sucking and breathing. Older children may demonstrate exercise intolerance. Both lungs are usually affected by the paradoxical motion. On inspiration, the eventrated diaphragm rises, which causes the mediastinum to shift and compress the contralateral lung.

Eventration is typically suspected on a plain radiograph when an elevated hemidiaphragm is seen (Fig. 24-11). The diagnosis is subsequently confirmed by ultrasonography or fluoroscopy. Motion studies demonstrate a paradoxical movement of the diaphragm during respiration with a shift of the mediastinum. Prenatal diagnosis of congenital eventration has been reported using fetal ultrasonography and MRI. Occasionally, CT is required to distinguish eventration from pleural effusions, mediastinal tumors, bronchogenic cysts, and pulmonary sequestrations.

Small eventrations may be left untreated. Eventually, the child will overcome and compensate for the abnormal diaphragmatic dynamics. Initial treatment should include respiratory support, but mechanical ventilation is usually not necessary. However, larger defects that cause functional pulmonary impairment or promote recurrent infections should be repaired. Neonates with large eventrations benefit from early repair rather than a course of conservative treatment. Acquired eventrations may require repair for the patient to be weaned from mechanical ventilation.

Surgical repair can be accomplished through the chest or abdomen. The eventrated diaphragm is plicated with a series of nonabsorbable sutures. The sutures should imbricate generous amounts of the diaphragmatic tissue without injury to the phrenic nerve. Edges of the diaphragm should overlap until the plicated muscle is taut. Subsequently, the diaphragm becomes immobilized, resulting in an increased tidal volume and preventing mediastinal shift. Minimally invasive techniques have been well described using thoracoscopic and laparoscopic approaches.