Increasingly, the diagnoses of chest lesions in infants are made not by symptoms of respiratory distress but by prenatal imaging. Because the availability and quality of prenatal imaging have increased, so has the frequency of prenatal diagnoses that include symptomatic and asymptomatic lesions. Early prenatal diagnosis of life-threatening lesions, such as congenital diaphragmatic hernia (CDH) and congenital cystic adenomatoid malformation (CAM or CCAM), allows detailed evaluation and subspecialty referral but may lead to decisions for pregnancy termination. It is imperative that counseling physicians have accurate and up-to-date information about prognosis in these difficult situations. Improved prenatal imaging also identifies lesions that may resolve spontaneously or may otherwise remain asymptomatic. As we gain in understanding of the natural history of these lesions, the advisability of routine surgical resection of asymptomatic lesions can be evaluated better.

This article discusses the embryologic development, diagnosis, treatment, and outcome of CDH and lung lesions of infancy. The focus is primarily on recent developments in the last decade and addresses areas of evolving controversy. Earlier writings are cited as needed to illustrate important historical points, identify concept development, and re-evaluate outdated thinking.

**Embryology and animal models of lung and diaphragm development**

Recent work in animal models has advanced our understanding of lung and diaphragm embryology. Although starting from different pathways and anlages, diaphragm and lung development are interrelated. Lung and
airway epithelium first arise as two small buds of endodermally derived foregut cells, whereas the rest of the foregut separates longitudinally into esophagus and trachea [1]. Extralobar pulmonary sequestration is thought to arise when collections of cells with respiratory potential arise from the primitive foregut distal to the lung buds, which gives rise to systemic blood supply and often systemic venous drainage. CCAM arises secondary to abnormalities in the signaling pathways between the developing terminal bronchioles and the supporting mesenchyme. Congenital lobar emphysema results from partial or complete obstruction of a lobar feeding bronchus, seemingly related to deficient cartilaginous support of that bronchus. Complete pulmonary agenesis, although a rare occurrence, is frequently associated with other foregut abnormalities, including tracheoesophageal anomalies [2–6], other VACTERL associations [7,8], and ipsilateral radial ray anomalies [9].

The diaphragm forms from the fusion of the septum transversum, the paired pleuroperitoneal membranes, the mesenchyme that arises adjacent to the esophagus, and the ingrowth of muscles from the body wall [10–12]. Defects in fusion of these components were believed to give rise to the various diaphragmatic defects encountered. Babiuk et al used immunohistochemical markers of muscle precursors in conjunction with mutant mice to examine phrenic-diaphragm embryogenesis [13]. They found that myogenic cells and axons coalesce within the pleuroperitoneal fold and, contrary to previous explanations, they expand to form the neuromuscular component of the diaphragm. They found no contributions to the diaphragm from the lateral body wall, septum transversum, or paraesophageal mesenchyme. CDH in the rat model resulted solely from defects in the formation of this mesenchymal substratum in the pleuroperitoneal fold.

The relationship between the developing diaphragm and lung has been the subject of intense laboratory effort. In CDH, the question involves which comes first, the diaphragmatic defect or the lung hypoplasia. The most studied and cited model of CDH is the nitrofen rat model. Nitrofen (2,4 dichlorophenyl-p-nitrophenyl ether) exerts a teratogenic effect when given to pregnant rats between 9 and 11 days’ gestation and results in a high incidence of CDH in offspring. In this model, pulmonary hypoplasia occurs earlier in development than would be expected by compression from the CDH contents alone, and from this finding has arisen the postulate that lung hypoplasia is the primary event in the development of CDH. Keijzer and colleagues [12] have shown that nitrofen exerts a direct negative effect on the developing lung because it interferes with branching morphogenesis and attenuates epithelial cell differentiation and proliferation in exposed lungs. This effect is additional to and separate from the mass effect exerted by abdominal contents on the developing lung after defective development of the diaphragm. Babiuk and colleagues [13] elegantly showed that CDH in the nitrofen model occurs in the amuscular mesenchymal component of the primordial diaphragm and is not related to abnormal muscle formation. More importantly, the diaphragm defect is not secondary to a defect of lung
formation and occurs independently of abnormal lung development. These data support the finding that in the nitrofen rat model of CDH, the diaphragm defect is a primary event and does not arise secondary to lung hypoplasia. This finding is consistent with commonly held thought regarding CDH in humans. In comparing the rat model and the human condition, it is important to remember that a teratogen causes CDH in this rat model, and no teratogen has been implicated in human CDH.

CDH also can be induced in rats by providing a vitamin A–deficient diet [14]. The retinoid hypothesis in the development of CDH is supported by many experimental observations, including the development of CDH in mutant mice that are deficient in cellular retinoid receptors. The incidence of CDH in the nitrofen rat model can be decreased by the specific administration of vitamin A [15,16]. Vitamin A also attenuates the lung hypoplasia seen in this model by blocking the development of lung hypoplasia early in gestation [16]. In humans, a single study showed that markers of vitamin A status were decreased in infants who had CDH compared with controls [17], but these findings have yet to be duplicated. A review of the experimental evidence regarding lung and diaphragm development is presented in more detail by Rottier and Tibboel [18].

### Congenital diaphragmatic hernia in humans: genetics

The cause of CDH in humans is not known. Although genetic influences are clearly important, specific information is limited. Structural chromosomal abnormalities are common in prenatally diagnosed CDH, and they occurred in 10% and 34% of prenatally diagnosed patients in two reviews [19,20]. CDH has been associated with abnormalities on nearly every chromosome, but it most commonly occurs with chromosomal duplications or deletions, including Turner syndrome (monosomy X), Down syndrome (trisomy 21), Edward syndrome (trisomy 18), and Patau syndrome (trisomy 13) [19–21]. Pallister-Killian syndrome (tetrasomy 12p) also is frequently encountered [22,23]. CDH can occur as part of a syndrome caused by a known gene, as in Denys-Drash syndrome (WT1) [19], Simpson-Golabi-Behmel syndrome (GPC3) [24], craniofrontonasal syndrome (EPNB 1) [25], neonatal Marfan syndrome (FBN1) [26], and spondylolisthesis (DLL3) [27]. Most cases of CDH, however, occur as isolated nonsyndromic presentations. Familial occurrences have been described, and the risk of a second occurrence with an otherwise negative family history is estimated to be 2% [28,29]. The existing knowledge on this subject recently was reviewed by Slavotinek [21].

### Prenatal diagnosis and markers of severity

The severity of CDH is a wide spectrum, and an understanding of the correlation between prenatal findings and clinical prognosis is vital for
counseling families accurately. Unfortunately, there is variable congruence between the prenatal imaging and resultant clinical picture, and differences in treatment and outcome at different centers blur the validity of prognostic variables. It is clear, however, that improved imaging has led to an increase in prenatal diagnosis of this disorder. Accurate prenatal imaging is important to identify associated anomalies and assess anatomic severity. Two-dimensional ultrasound continues to evolve, and three-dimensional ultrasound and MRI have been added to the diagnostic armamentarium [30–34]. Associated anomalies are present in a high percentage of fetuses, approaching 40% in two separate studies [35,36]. Such anomalies have been thought to compromise survival [35], but it is increasingly clear that most associated anomalies, such as atrial septal defect (ASD), malrotation, Meckel’s diverticulum, and unilateral kidney, should have little effect on survival. Chromosomal anomalies and serious heart defects are exceptions and negatively affect survival. Graziano [37] reviewed the experience of the CDH Study Group and found that of 2636 patients reported, 280 (10.6%) had significant heart defects, of which ventricular septal defect (VSD) was the most common (42.2%) (Fig. 1). Overall survival rate for CDH was 67% but dropped to 41% in the heart defect group (Fig. 2). Patients with univentricle anatomy and CDH had only a 5% survival rate.

Fig. 1. Types of cardiac defects observed in patients who have CDH and congenital heart disease (n = 280). (From Graziano JN. Cardiac anomalies in patients with congenital diaphragmatic hernia and their prognosis: a report from the Congenital Diaphragmatic Hernia Study Group. J Pediatr Surg 2005;40(6):1046; with permission.)
Numerous attempts have been made to correlate prenatal imaging with postnatal outcome in patients without associated life-threatening anomalies, but with mixed results. The lung-to-head ratio (LHR), first described by Metkus and Harrison in 1996 [51], is an attempt to report two-dimensional lung size in the fetus relative to a growth standard (head circumference) and correlate the finding with outcome. In their initial prospective report of 15 patients, LHR was measured at 24 to 26 weeks. No patient with an LHR less than 1 survived ($n = 3$). All patients with LHR more than 1.4 survived, and survival rate was 38% when the LHR was 1.0 to 1.4. Overall survival rate in the 15 patients was 47%. LHR seemed to be validated by Laudy and colleagues [38] in a review of 26 patients, which showed 100% survival rate if the LHR was more than 1.4, regardless of gestational age at testing. Survival rate for the series was 50%. Heling and colleagues [39] were unable to correlate LHR with survival.

MRI and three-dimensional ultrasound have been used to calculate three-dimensional lung volumes in fetal CDH, and researchers have compared the
validity of these measurements to two-dimensional LHR. Ruano and colleagues [40] showed good correlation between MRI and three-dimensional ultrasound measurements of lung volume in CDH and demonstrated that patients who died of CDH had a lower range of measured lung volumes than survivors [30]. As expected, MRI was useful for diagnosing fetal CCAM, chylothorax, and esophageal atresia [41].

Liver position on prenatal imaging, either entirely abdominal or partly intrathoracic, also has been described as a measure of severity [42]. Data from the CDH Study Group demonstrate that 75% of all patients who have CDH have some portion of liver in their chest [43], which suggests that this is not a sufficiently discriminating observation. Perhaps the volume or fraction of liver in the chest may be a more specific predictor of outcome.

Other risk factors that have been variably shown to predict poor outcome include the antenatal factors of prenatal diagnosis, polyhydramnios, and right-sided defect [44–46]. Similarly, postnatal factors, such as poor aeration on chest radiograph [47], also have been shown to correlate with poor outcome. Each of these factors has failed validation when tested in later studies, however [48–50], even when re-evaluated at the same center [51]. Great caution should be used in citing and interpreting these risk factors during counseling of families with a fetal diagnosis of CDH.

Two studies have correlated successfully early postnatal physiologic measurements with outcome. The Congenital Diaphragmatic Hernia Study Group developed an equation for predicting survival based on birth weight and 5-minute Apgar score [52], and the Canadian Neonatal Network validated the SNAP-II score as predictive of mortality in CDH in their population of 88 patients [53]. These objective evaluations allow better stratification of illness severity in series and have been used to provide evidence of improved survival with evolving treatment strategies [5].

Treatment and outcome

Infants born with CDH face fundamental physiologic problems, including pulmonary hypoplasia and pulmonary hypertension. Historically, efforts to improve survival have focused primarily on one or the other of these aspects.

Prenatal interventions

Because of the low CDH survival rates of only 20% to 42% experienced in the late 1980s and early 1990s [44,54], Harrison and others [55,56] pursued in utero surgical interventions to promote lung growth. After initial animal studies, the first open human fetal repair of CDH was performed by Harrison in 1990. Eventually 21 fetuses underwent open fetal repair
but only 5 survived [57,58]. Some fetuses showed evidence of lung growth, but technical complications and premature labor resulted in poor outcomes for most patients. Open fetal repair for CDH was abandoned.

After the failure of open fetal repair to improve survival, surgical fetal interventions for CDH took a new direction. Congenital laryngeal atresia was recognized to cause large fetal lungs. Based on this and other observations, Wilson and colleagues [59] and DiFiore and colleagues [60] demonstrated that fetal tracheal occlusion prevented fetal pulmonary hypoplasia in a fetal lamb nephrectomy model and resulted in increased lung growth in the fetal lamb CDH model. Harrison and colleagues [61] applied this concept to human fetuses with CDH in an attempt to promote lung growth and improve survival. Three approaches eventually were used, including open fetal tracheal ligation, fetoscopic tracheal clipping, and fetoscopic tracheal occlusion by a detachable balloon. Open fetal tracheal ligation was met with poor survival, and fetoscopic tracheal ligation showed better survival but with significant tracheal morbidity, including several patients with bilateral recurrent laryngeal nerve injuries. Fetoscopic tracheal occlusion showed the most promise [62], and in 2003, Harrison and colleagues [63] reported the results from a National Institutes of Health–sponsored trial that compared fetoscopic tracheal occlusion with standard postnatal care. Entry criteria included left CDH with some degree of liver herniation into the chest and LHR less than 1.4. Twenty-four patients were randomized, but the trial was stopped before completion. Eight of 11 treated fetuses survived (73%), but because of continued improvement in standard postnatal care, 10 of 13 (77%) control patients also survived. Despite a great deal of effort, fetal surgical interventions for CDH failed to show an improvement in survival and cannot be recommended at this time.

Postnatal management

The last decade of postnatal CDH management has shown an ongoing search for a magic bullet. As with prenatal interventions, early excitement about the use of extracorporeal membrane oxygenation (ECMO) [64,65], delayed surgery [66–68], surfactant [69], nitric oxide [70], and even sildenafil [71,72] has been tempered by subsequent reports that cast doubt as to the survival benefit of these therapies. Despite several studies that showed dramatic improvements in survival with changed therapeutic strategy [48,73], other reports discount those claims [74,75]. Survival reported by the CDH study group has continued to improve from 63% reported in 1998 [76] to 67% reported in 2005 [37].

Postnatal outcome of CDH treatment varies from center to center, even in the same facility over time as treatment strategy evolves. Reickert and colleagues [77] showed in 1997 that of 411 patients who had CDH and were treated at 16 different level-III neonatal intensive care with ECMO, survival
rate to discharge varied from 39% to 92%, and ECMO use varied from 32% to 60%. No effort was made to stratify the severity of CDH encountered at these centers, but it seems unlikely that this alone would account for the large differences in survival encountered. The CDH literature shows wide variation in treatment approaches at different centers, and differences in outcome are likely caused, at least in part, to differences in therapy. There remains a paucity of randomized and properly controlled trials in the CDH literature [78], which makes it difficult to compare differences in therapy. Much of current therapeutic strategies arise from an accumulation of observational data.

Delayed surgery

Repair of CDH was once a surgical emergency at birth, but stabilization and delay of surgical repair to 24 hours and beyond have been embraced enthusiastically. Pulmonary gas exchange often improves in the first 24 hours after birth, and respiratory compliance improves with preoperative stabilization [79]. Although there is no evidence that delayed repair is harmful, there is also no convincing evidence that such delay improves survival or decreases risk of pulmonary hypertension [80–83]. Because delay in surgery is not harmful, there is no compelling reason to perform emergent surgery at birth, and our practice is to delay operative repair of the CDH.

Surfactant

Although the lamb and rat models of CDH suggest surfactant deficiency [84–87], this is controversial in humans. Evaluation of bronchoalveolar lavage fluid analyzed for components of surfactant in infants with CDH showed no differences when compared with age-matched controls, which suggests that a primary surfactant deficiency is unlikely [88]. Surfactant kinetic studies in human infants with CDH compared with control infants found no differences in surfactant phosphatidylcholine pool size or half-life [89,90].

The Congenital Diaphragmatic Hernia Study Group is a multicenter international cooperative organization of tertiary referral centers that cares for patients who have CDH and shares their data through a voluntary database. Started in 1995, this database currently holds more than 2500 patients and has provided important information about CDH care and outcome, including surfactant use in term, preterm, and ECMO patients who have CDH [91–93]. Logistic regression or multivariate analyses were performed to adjust for differences in severity of illness between patients who receive surfactant and those who do not. Conclusions from these individual reports are as follows: (1) In term infants with CDH, the use of ECMO and development of chronic lung disease was higher and survival was lower in the surfactant-treated group of patients (Fig. 3). After adjusted logistic regression, the odds ratios generated showed no benefit to surfactant
therapy with regard to survival, need for ECMO, or development of chronic lung disease [91]. (2) In preterm infants, patients who received surfactant (209 patients) had a higher odds ratio of dying than those who did not receive surfactant (215 patients). Multivariate analysis to adjust for severity of illness did not change this result [92]. (3) In patients who had CDH and were on ECMO support, surfactant administration did not improve survival, shorten the ECMO run, or decrease the need for oxygen at 30 days compared with patients who did not receive surfactant [93]. Taken individually and together, these studies show no benefit to surfactant administration in patients with CDH, and there was potential for worse outcome in surfactant-treated patients.

**Nitric oxide**

As a powerful, relatively nontoxic therapeutic agent delivered by inhalation directly to the target organ, nitric oxide was expected to have a dramatic effect on pulmonary hypertension in CDH. Despite a rapid and sometimes dramatic effect on oxygenation when given to a patient with a pulmonary hypertensive crisis, inhaled nitric oxide has not been shown to improve survival or decrease the need for ECMO in a controlled trial of nitric oxide treatment in CDH [94]. Hyperventilation was used in most patients in this multicenter trial, and ventilator-induced lung injury could have masked a beneficial effect of nitric oxide. This outcome was different from that for newborns from
a separate arm of the same study who did not have CDH and who experienced a decreased need for ECMO when treated with nitric oxide [95]. Other investigators have reported good results using nitric oxide combined with high-frequency oscillatory ventilation in CDH but without adequate controls [96–98]. A Cochrane review in 2001 found no clear data to support the use of inhaled nitric oxide in infants who have CDH [99].

*Sildenafil*

Sildenafil is a specific phosphodiesterase-5 inhibitor shown to decrease pulmonary vascular resistance [100]. In a piglet model of meconium aspiration it was significantly more effective in ameliorating pulmonary hypertension than inhaled nitric oxide [101]. Oral sildenafil has been used in isolated, uncontrolled cases to treat neonatal pulmonary hypertension [102]. In patients who have CDH, oral [72] and intravenous [71] sildenafil has been used to treat pulmonary hypertension that is refractory to inhaled nitric oxide. Two patients had objective response, but only one recovered and survived. This medication may be of some unique benefit, but insufficient data exist currently. Study of this drug in a prospective, randomized fashion is indicated.

*Extracorporeal membrane oxygenation*

ECMO originally was used as rescue therapy in patients who had CDH with pulmonary hypertension after corrective surgery. Retrospective review of 730 neonates from the CDH Study Group treated from 1995 to 1997 showed that ECMO use was associated with improved survival when used in patients who had CDH and had a predicted mortality of ≥ 80% [103]. This benefit was not evident when ECMO was used in patients with less severe disease. As therapies have evolved, the timing of ECMO support has changed. In 1995, 20% of ECMO use in patients who had CDH was postoperative, but by 2001 this use had declined to only 5% [104], which illustrated the trend to preoperative stabilization with ECMO rather than postoperative rescue. By 2002, there were 2077 patients in the CDH registry, and 770 had been treated with ECMO (37%). Despite widespread acceptance and use, however, a Cochrane review concluded that ECMO offers short-term benefits for babies with diaphragmatic hernia, but the overall effect of using ECMO in this group remains unclear [105].

The mode of ECMO support for CDH patients also has been evaluated. Dimmitt reviewed the ELSO registry for the 1990s and reported in 2001 that veno-arterial (VA) ECMO was used in 86% of patients who had CDH compared with only 14% who received veno-venous (VV) support [106]. The pre-ECMO status was similar in the groups, although the VV group received more pressors and more frequent use of surfactant and nitric oxide. Survival was not different (58% for VV ECMO and 52% for VA; \( P = 0.57 \)) but seizures were more common in the VA group (12.3% versus 6.7%);
\( P = 0.0024 \), as was cerebral infarction (10.5% versus 6.7%; \( P = 0.03 \)). Sixty-four patients were converted from VV to VA (17%) and the survival rate was less (43.8%) but not significantly so. The authors concluded that VV ECMO for CDH had similar survival rates to VA ECMO but with less neurologic morbidity, and they saw no disadvantage to VV ECMO as the initial mode of ECMO support in CDH. These findings mirrored those of Schmidt and colleagues [107] and Kugelman and colleagues [108] in their single institution reviews.

Despite ongoing, widespread use of ECMO in CDH, there are reports of centers using ECMO significantly less frequently in their populations while still achieving high survival rates. Some centers report ECMO use in less than 15% of patients who have CDH [50,109]. These centers exclude a small proportion of severely ill infants from ECMO who meet institutional criteria for lethal pulmonary hypoplasia. They also have significant outborn populations, which exerts a selection bias, because the most severe outborn patients do not survive transfer into the accepting center. These centers’ excellent survival rates, while using ECMO sparingly, again raise the question of benefit of ECMO in patients who have CDH.

**Lung distension in congenital diaphragmatic hernia**

Liquid perfluorocarbons possess unique physical properties, including high density, ability to carry oxygen and carbon dioxide, and low surface tension, which may prove useful in the ventilation of patients who have CDH and other forms of respiratory failure. A report in 2001 showed that distension of CDH lungs with perfluorocarbon on ECMO seemed to accelerate lung growth in five patients who had CDH and were on ECMO and improved subsequent gas exchange off ECMO [110]. A prospective, randomized pilot study of this therapy was published in 2003 in which eight patients who had CDH and were on ECMO were treated with perfluorocarbon instillation into their lungs to 5 to 8 cm of water compared with standard conventional ventilation on ECMO [111]. Study subjects realized nonstatistically significant improvements in time on ECMO, ventilator-free days, and survival compared with controls. A more definitive trial of this novel intervention is warranted and may hold the most promise for patients who have severe pulmonary hypoplasia.

**Ventilation**

Hyperventilation and induced alkalosis to decrease pulmonary hypertension and control ductal shunting were common therapeutic strategies in the late 1980s and 1990s and still are used in many centers. These therapies never showed improved survival, and studies of CDH mortality showed that pulmonary barotrauma, as evidenced by diffuse alveolar damage,
hyaline membrane formation, pneumothorax, pulmonary hemorrhage, and occasionally even interstitial fibrosis, was the dominant finding at postmortem examination [73,112]. Iatrogenic barotrauma represented a potentially avoidable cause of mortality in patients who had CDH and was postulated to contribute to 25% of CDH deaths [73].

The single most significant advance in the management of patients who have CDH in the last 20 years has been the development and propagation of a neonatal ventilation strategy that significantly limits inflation pressure, allows tolerance of hypercapnia and relative post ductal hypoxemia, and eliminates hyperventilation. The gentle ventilation strategy was pioneered by Wung and colleagues [114], first in neonates with pulmonary hypertension who did not have CDH [113] and then in neonates who had CDH. This strategy, especially the tolerance of hypercarbia in pulmonary hypertension, ran counter to conventional wisdom and was not quickly accepted into practice [115]. Validation of concept and results were reported by Wilson [73] and Kays, however [48]. Detailed ventilation analysis of 89 patients showed that pneumothorax rates plummeted (from 43% to 2%) and survival rates improved dramatically (from 50%–89% in treated patients) with the introduction of a lung protective strategy that avoided hyperventilation and limited inflation pressures to ≤25 cm of water [48]. Other researchers have reported similar series [5,50,116], and survival rates of more than 80% in patients with isolated CDH have been achieved in several centers using gentle ventilation.

**High-frequency oscillatory ventilation**

High survival rates in CDH have been achieved by some investigators using high-frequency oscillatory ventilation [97,98,117], but others report no improvement in outcome compared with management with conventional ventilators [118–120]. The question of whether high-frequency oscillatory ventilation is best used as rescue if conventional ventilation fails or should be a primary mode of ventilation is not clear. It is clear, however, that barotrauma, which most frequently presents as pneumothorax but manifests in other aspects of lung failure, is associated with decreased survival in CDH [48,121,122]. Lung protective ventilation, whether by conventional mechanical ventilation or high-frequency oscillatory ventilation, must be provided to optimize CDH survival. A clear and unwavering treatment strategy that protects every alveolus with which patients who have CDH are born, is the closest we can come to a magic bullet in CDH.

**Outcomes**

An improved understanding of CDH pathophysiology and expanded application of lung protective treatment strategies has led to an improved
CDH survival rate. Infants who survive CDH are at risk of brain injury, [123] neurodevelopmental disability [124], hearing loss [125,126], feeding difficulties [127], gastroesophageal reflux [128,129], lung disease [130], scoliosis [131], pectus excavatum [131], and recurrence of their diaphragmatic hernia. Some of these outcome issues are anatomic and unavoidable. Other outcome issues reflect potential toxic effects of treatment strategies and may be avoided or eliminated in the future.

Although most infants who have CDH survive without major neurologic sequelae, newborns who have more severe CDH have small lungs and are at risk for periods of hypoxemia, acidosis, poor perfusion, and need for ECMO. These more severely affected infants are at high risk for hypoxic-ischemic brain injury and other secondary neurologic effects of severe illness. A review of 31 patients who had CDH who also required ECMO showed that 35% had central nervous system abnormalities on CT scan, which manifested primarily as enlarged ventricles, focal and diffuse brain atrophy, and intracranial hemorrhage. At 2 years, these patients showed mild cognitive and physical delay [124]. MRI at discharge showed evidence of brain injury in eight of eight CDH survivors, including some with relatively mild CDH [132]. In three separate series, 44% to 55% of CDH survivors required hearing amplification because of hearing loss [133–135]. It is important to note that many of these survivors came from the era of hyperventilation.

**Neonatal lung anomalies**

Fetal lung lesions may cause significant mass effect, result in nonimmune hydrops, and lead to fetal or infant demise. Therapeutic options for these severely affected infants are evolving. The abundant use of prenatal imaging also has led to the identification of small fetal lung lesions that may be asymptomatic at birth and beyond. Management of these lesions is not clear.

**Prenatal diagnosis and interventions**

Prenatal diagnosis of CCAM, pulmonary sequestrations, and congenital lobar emphysema are the subject of an evolving literature. Ultrafast fetal MRI after initial identification of a chest lesion by two-dimensional ultrasound is reported to be a useful and important adjunct. MRI has been shown to confirm ultrasound diagnosis, provide more detailed anatomic information, and achieve greater diagnostic accuracy than ultrasound alone [41,136,137]. Three-dimensional ultrasound also offers more detailed imaging and was tested in eight cases of hyperechogenic fetal lung lesions, correctly identifying the abnormal feeding vessel in all three cases of pulmonary sequestration and showing no such vessel in the five CAMs [138]. Postnatally, CT and MR angiography have been used to identify anomalous systemic feeding vessels in pulmonary sequestrations with high
accuracy [32,139–141], and these imaging advances obviate the need for more invasive angiography.

Fetal lung lesions can lead to nonimmune hydrops. Of 175 prenatally diagnosed lung lesions reported by Adzick and colleagues [142], 134 were CCAMs. All of the fetuses without hydrops survived, whereas all 25 with hydrops who did not undergo some type of fetal intervention died. Thirteen women with hydropic fetuses underwent open fetal surgery; eight fetuses survived. Six fetuses with a large unilocular pulmonary cyst had percutaneous placement of a thoracoamniotic shunt, and five survived.

Forty-one of the 175 lesions were extralobar pulmonary sequestrations. Twenty-eight of these regressed dramatically on prenatal studies, were asymptomatic at birth, and were later identifiable only by CT or MRI. None of these was resected. Of the remaining 13 fetuses with extralobar sequestrations, 2 aborted electively, 1 developed hydrops and died, 3 had hydrothorax treated with prenatal drainage procedures, and 7 were symptomatic postnatally and underwent resection.

The size and follow-up of this study warrants attention. The authors stressed the poor prognosis in patients with nonimmune hydrops secondary to fetal lung lesions when only followed expectantly. Survival with fetal intervention was superior in patients who had CCAM and nonimmune hydrops. Of note, the details of postnatal ventilatory support in the children who died were not provided.

An expanded experience with thoracoamniotic shunting for fetal pleural effusion and CCAM was reported in 2004 [143]. This procedure seems to play a beneficial role for the fetus with a large CCAM or sequestration with associated large hydrothorax and secondary nonimmune hydrops but may be complicated by preterm delivery [144].

Although the development of nonimmune hydrops with prenatal CCAM is clearly a marker of severity, others have not found the association universally fatal, even without fetal therapy. Ierullo reported [145] 34 cases of prenatal CCAM, and 76% improved or resolved during prenatal monitoring, including resolution of hydrops in 3 of 6 cases. Illanes reported [123] 48 cases of prenatal lung lesions, with hydrops in 9. Of these fetuses, three survived, whereas six progressed and resulted in fetal or infant demise. The Fetal Therapy group at the University of California at San Francisco reported three prenatally diagnosed fetuses with CCAM and hydrops who were treated with maternal steroids in the second trimester. All three patients enjoyed resolution of the hydrops and delivery at term without respiratory distress [146].

**Postnatal management**

Symptomatic lung lesions in infants and children warrant resection. Lobectomy is the procedure most frequently used and results are excellent, with minimal morbidity and mortality in experienced hands [147,148].
Symptomatic lesions are resected when indicated, either at presentation or after a period of treatment (ie, antibiotics for infection).

Management of asymptomatic lung lesions in infants and children remains controversial. Authors who favor resection of prenatally diagnosed but asymptomatic lung lesions favor resection before 1 year of age [81,149,150]. Adzick recommends resection after 1 month of age, whereas Laberge recommends no later than 3 to 6 months to maximize potential for compensatory lung growth [149,150]. Thoracoscopic techniques are also used for anatomic pulmonary resections, even in infants [151,152], and their applicability is likely related to the experience level of the surgeon.

**Cystic adenomatoid malformation**

The natural history of the asymptomatic CCAM found by prenatal imaging is not clear. Although most authors favor resection of symptomatic and asymptomatic CCAM [148–150,153], there is an increase in the number of series reporting careful follow-up and expectant management in asymptomatic lesions. Series that favor resection cite that CCAM eventually becomes infected in most cases [149] and has an associated risk of malignancy, including rhabdomyosarcoma [154,155], pleuropulmonary blastoma [156], and bronchoalveolar carcinoma [157]. Series that favor observation of asymptomatic lesions cite that malignancy is rare, the true incidence of infection in asymptomatic lesions is not known, and a single incidence of previous infection does not result in an increase in operative complications [81]. Reports of apparent spontaneous resolution of CCAM during gestation and postnatally add support to the nonoperative strategy. Prenatally diagnosed CCAM resolved spontaneously during gestation at a rate of 15% to 30% in recent representative series [158,159]. Plain chest radiography is not sufficiently sensitive to define this, and postnatal CT is required to confirm resolution of the CCAM. Postnatal resolution of CCAMs also occurs but much less commonly, and it occurred in only 2 of 56 cases (4%) reported by Butterworth and Blair [160].

Two recent studies reported observation alone of asymptomatic CCAM. Van Leeuwen and colleagues reported 14 cases in 1999 [161]. Four patients were symptomatic at birth and underwent resection and 10 were asymptomatic. Five received or were due for elective resection (based on surgeon preference), whereas 5 others were observed for 36 \( \pm \) 15 months without adverse sequelae. Aziz and Langer [81] reported on 35 asymptomatic patients who had CCAM. Fifteen asymptomatic patients underwent elective resection—6 patients before and 9 patients after 6 months. Three patients developed symptomatic infection between 6 and 12 months and underwent resection. Seventeen remained asymptomatic without resection at a median follow-up of 3 years. These data suggest that nonoperative management of CCAM remains controversial even in centers that practice it, with a significant proportion of asymptomatic patients receiving elective resection.
Infection that led to resection developed in 10% of asymptomatic children during observation [81].

Pulmonary sequestration and congenital lobar emphysema

These lesions have a highly favorable prognosis when diagnosed prenatally compared with CCAM, and survival is excellent [142,162]. Hydrops occasionally can result. Both lesions may resolve during gestation and the postnatal period. Congenital lobar emphysema may improve with bronchial development. Although symptomatic lesions warrant aggressive surgical management, observation of asymptomatic patients is more commonly practiced in these lesions than CCAM [149,150].

Summary

CDH and neonatal lung lesions are increasingly diagnosed during fetal life, and expanded use of three-dimensional ultrasound and fetal MRI have improved diagnostic detail and accuracy. Chromosomal abnormalities and severe congenital heart lesions negatively impact CDH outcome, but survival at several centers that have abandoned hyperventilation in favor of strict lung protective strategies exceeds 80% in patients who have isolated CDH. Congenital lung lesions range from small, asymptomatic imaging abnormalities to large, space-occupying lesions that cause fetal hydrops. Symptomatic lesions should be resected during infancy, and resection remains the standard for most asymptomatic lesions. Increasing numbers of reports indicate that small, asymptomatic lesions are being treated with observation and follow-up alone, and maturation of this literature is expected in the years to come.

References


