Congenital Diaphragmatic Hernia: Real Improvements in Survival

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Author Disclosure
Dr Kays did not disclose any financial relationships relevant to this article.

Objectives

After completing this article, readers should be able to:

1. List the anomalies associated with congenital diaphragmatic hernia (CDH).
2. Delineate methods of determining the severity of CDH.
3. Review the roles of exogenous surfactant, extracorporeal membrane oxygenation, inhaled nitric oxide, sildenafil, and gentle ventilation in the management of CDH.
4. Describe the surgical repair undertaken in CDH.

Introduction

Congenital diaphragmatic hernia (CDH) is an intellectually fascinating and challenging birth defect that too often results in tragic loss for the child and family. Frequently diagnosed ultrasonographically at 20 weeks' gestation, the diagnosis can overwhelm affected parents who never knew the condition existed and seldom can understand it adequately. Affected newborns face myriad potential issues, including pulmonary insufficiency, pulmonary hypertension, hemodynamic instability, associated cardiac defects, eventual feeding difficulties, and significant risk of dying or of surviving with substantial morbidity. Well-meaning but often inadequately informed physicians and caregivers too frequently view the situation as either hopeless or requiring dramatic but completely unproven prenatal interventions. However, improvements in understanding of CDH physiology coupled with expanding recognition of the negative effects of previously standard postnatal therapies have led to dramatic improvements in CDH survival in many centers. Some argue that the impact on overall CDH survival from these "advances" has been nil, but this is, in large part, due to continued significant rates of pregnancy termination with this diagnosis, rapid adoption of adjuvant CDH treatments, and slower penetration of fundamental changes in CDH therapy.

This review examines what is known of the etiology of CDH, details the factors that affect the severity of the condition, describes the pathophysiology facing affected newborns, defines the physiologic basis of modern treatment, and provides examples of the improved survival and outcome experienced at centers that have embraced certain fundamental concepts.

Epidemiology and Etiology

A relatively common birth defect, CDH is estimated to occur once in every 2,500 to 3,000 live births. Based on the 2003 United States birth rate of 4,091,063, approximately 1,500 to 1,600 newborns have CDH annually. Allowing for an optimistic overall survival rate of 60% among babies brought to term and accounting for at least a 15% prenatal termination rate, at least 750 babies are estimated to die from CDH in the United States each year. For comparison, 500 children are diagnosed yearly in the United States with Wilms tumor, of whom fewer than 150 die, and 800 newborns are born with gastroschisis, of whom fewer than 100 die. The contrast with the 750 deaths due to CDH clarifies the importance and magnitude of this diagnosis.

Although the cause of CDH is not known, it likely represents the end result of one or more genetic defects. CDH has been associated with abnormalities on almost every human chromosome, and overt chromosome abnormalities were seen in 10% and 34% of affected patients reviewed by Witters and Howe. (1)(2) When CDH occurs as part of a syndromic presentation stemming from abnormal chromosomes, it most commonly occurs with

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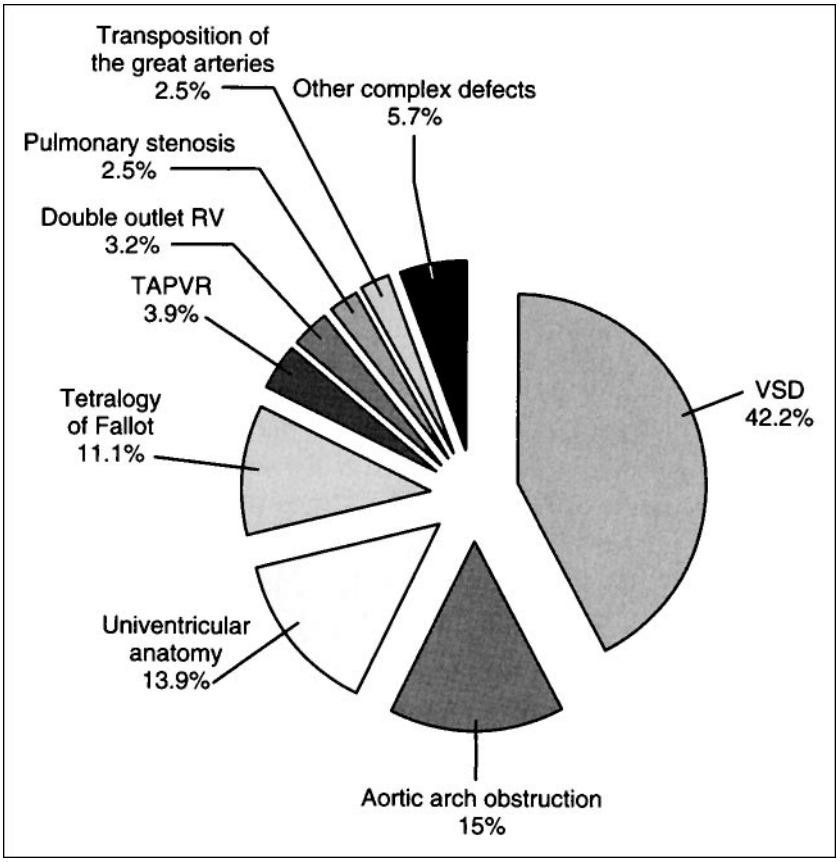

Figure 1. Anomalies associated with CDH. Reprinted with permission from Graziano JN. (3)

problems of chromosome number, as in Turner syndrome (monosomy X), Down syndrome (trisomy 21), Edward syndrome (trisomy 18), and Patau syndrome (trisomy 13). CDH also occurs frequently in Pallister-Killian syndrome (tetrasomy 12p). CDH also can present syndromally based on a known single gene abnormality, as in Denys-Drash syndrome (WT1), spondylocostal dysostosis (DLL3), and neonatal Marfan syndrome (FBN1), among others.

Most cases of CDH, however, occur as isolated events in nonsyndromic presentations. No unifying gene abnormality has been identified in these cases thus far. The risk of having a second affected child after a first nonsyndromic presentation is estimated at 2%, a 50-fold increase from the estimated baseline risk of 0.04% (1:2,500).

Associated Anomalies

Associated anomalies occur commonly in CDH, at a reported rate of nearly 40% in two separate studies, but most of the anomalies have minimal if any effect on survival. For example, atrioseptal defect (ASD), malrotation, Meckel diverticulum, undescended testes, and unilateral kidney have no appreciable effect on neonatal survival of infants who have CDH.

Associated anomalies that clearly affect survival include chromosomal anomalies and serious heart defects. Graziano (3) reviewed the experience of the CDH Study Group and found that of 2,636 patients reported, 280 (10.6%) had significant heart defects, of which ventricular septal defect (VSD) was the most common (42.2%) (Fig. 1). The overall survival rate for CDH in that report was 67%, but decreased to 41% in the group that had heart defects. VSD alone had only a small effect on survival, but more complex defects had larger effects. Univentricular anatomy in the face of CDH was associated with less than 5% survival, and there were no survivors of CDH coupled with transposition of the great arteries (Fig. 2).

CDH, even in its isolated form, represents a spectrum of disease, from very mild in which the presentation may be delayed for years, to very severe in which the child may not survive to leave the delivery room. The majority (80%) are left-sided. Previously it had been said that most children afflicted with CDH do not have sufficient lung to survive, but it has been my and other's experience that the opposite is true. It has become increasingly clear that the addition of iatrogenic lung injury to the condition of pulmonary hypoplasia seen in CDH can easily convert survival to death. The challenge, therefore, is to find the least toxic treatment and support strategy for affected children to optimize both the quantity and the quality of outcomes. The evolution of treatment strategies that minimize or eliminate the detrimental effects of previously standard therapies, such as hyperventilation, have allowed dramatic improvement in outcome. (4)

Pathophysiology

Babies born with CDH face fundamental physiologic problems. Herniation of abdominal contents into the chest of the developing fetus compresses the developing

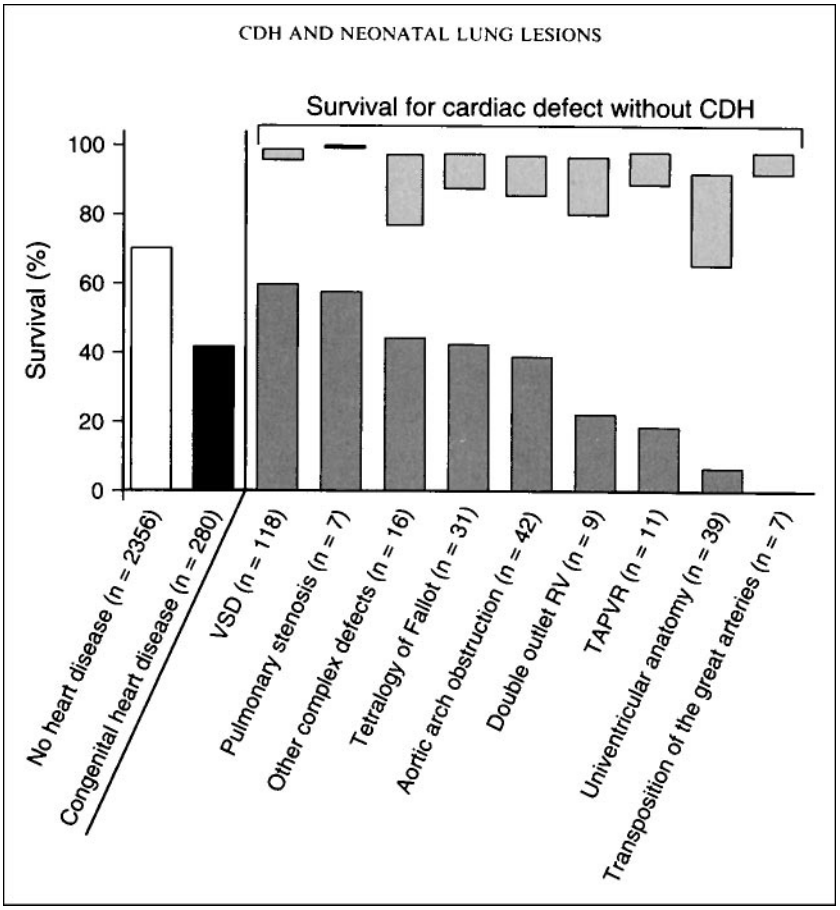

Figure 2. Survival rates of infants who have CDH and associated cardiac anomalies. Reprinted with permission from Graziano JN. (3)

lungs, with the larger defects and earlier herniations having greater effects on the developing lungs. The resulting pulmonary hypoplasia is a spectrum, and although size is helpful, it also is important to realize that lungs are dynamic, metabolically active organs that have the ability to effect gas exchange that relates to more than just size.

Markers of Severity

Because survival in affected neonates relates to more than just lung size, attempts to predict patient survival based on lung size alone, either by prenatal evaluations such as ultrasonography or magnetic resonance imaging (MRI), or postnatally based on findings on chest radiography have had limited success. The lung-to-head ratio (LHR) originally described by Metkus and associates in 1996 (5) and still used today is an attempt to correlate measured right lung size in the fetus that has left-sided CDH to a growth standard (head circumference) and to correlate the relative lung size with outcome. In their original study of 55 patients, LHR was measured at 24 to 26 weeks' gestation and tested retrospectively. Based on the findings in these 55 patients, the LHR was tested prospectively on the next 15 patients and ranged from 0.62 to 1.86. None of three patients who had LHR of less than 1.0 survived, three of eight who had LHR of 1.0 to 1.4 survived, and four of four who had LHR of greater than 1.4 survived. Other authors have attained variable results when attempting to correlate LHR with survival.

Several researchers have used newer technologies such as three-dimensional ultrasonography and MRI to calculate measured fetal lung volume. Such reports, like those of LHR, show significant overlap between the range of survivable and nonsurvivable lung size. This finding verifies that although it is beneficial to have more rather than less lung, survival alone rests on many additional variables beyond lung size. Until variables such as lung function, tenacity of pulmonary hypertension, standardization of treatment variables, and elimination of treatment complications are controlled satisfactorily, measurement of lung size alone is inadequate to predict survival reliably. Measuring prenatal lung size to help estimate disease severity, however, is useful in counseling families and in planning resuscitation, as long as the limitations of the measurement are considered.

Another valid method to estimate severity of CDH during prenatal and postnatal evaluations is to evaluate the extent of herniated abdominal contents. In a left CDH, herniation of intestine only into the chest, with stomach and liver in the abdomen, correlates with good lung development and adequate diaphragm for primary closure. Patients thus affected should do well, with minimal risk of mortality and need for extracorporeal membrane oxygenation (ECMO). Patients who have bowel and additionally stomach in the chest (which also includes the spleen), but liver in the abdomen have an

intermediate CDH with intermediate risk. Patients who have bowel, stomach, spleen, and liver in the chest have more severe CDH and are at significant risk for morbidity, mortality, and need for ECMO. Virtually all patients who have severe CDH have insufficient native diaphragm for primary closure and require a large patch. Patients at highest risk are those who have a large amount of liver in the chest and have a correspondingly low LHR.

Patients who have right-sided CDH also have a spectrum of disease, but virtually all have liver in the chest, although the presence of liver in this situation does not necessarily portend a poor prognosis. However, a patient who has a right-sided CDH and more than 50% of the liver in the chest, as evidenced by gallbladder in the chest on ultrasonography, is a challenge and likely will require ECMO. Other than LHR, which originally was described in left-sided CDH, markers of severity in right CDH are not as well defined.

An important exception to the anatomic description of severity that is virtually impossible to elucidate by prenatal imaging is the presence of a CDH "sac." When a completely attenuated remnant of diaphragm or peritoneal sac remains, the CDH pathophysiology is less severe than would be predicted by other measures of severity, such as herniated abdominal contents. It appears that the sac holds the abdominal contents back a bit or possibly the herniation occurred later in gestation. Regardless, the presence of a sac found at surgical repair correlates with less severe pulmonary hypoplasia and predicts an improved prognosis.

Fetal Surgical Intervention

Attempts to increase lung development and size by prenatal interventions have been evolving for nearly 20 years. The original concept was to repair the CDH in the fetus, return the fetus to the womb for further lung growth and development, and deliver the repaired fetus electively near term. After initial animal studies, the first open human fetal repair of CDH was performed by Harrison in 1990. (6) However, technical problems with the repair and ongoing problems with uterine irritability and preterm delivery took their toll on the outcome. Eventually, 21 fetuses underwent open fetal repair, but only five survived. (7)(8)

After this unsuccessful beginning, fetal interventions moved to techniques designed to occlude the fetal trachea. Obstruction of the normal egress of lung liquid from the trachea had been observed in experiments of nature, and later demonstrated in an animal model, to result in development of abnormally large lungs. When applied to the lamb model of CDH, affected lungs became distended and grew, even herniating down through the diaphragm defect. (9) Several technical modifications of this concept were applied to human fetuses affected by CDH, including tracheal ligation, occluding tracheal clips, and removable intratracheal balloons placed by fetoscopy. Open fetal tracheal ligation was associated with poor survival. Fetoscopic tracheal ligation resulted in better survival, but with significant tracheal morbidity, including bilateral recurrent laryngeal nerve injuries. Fetoscopic tracheal occlusion showed the most promise, (10) and in 2003, Harrison reported the results from a National Institutes of Health-sponsored randomized trial comparing fetoscopic tracheal occlusion in prenatally diagnosed CDH with standard postnatal care. (11) Entry criteria included left CDH with liver herniation and LHR less than 1.4. Twenty-four patients were randomized, but the trial was stopped early, with 8 of 11 trial patients surviving (73%) as well as 10 of 13 (77%) control patients. The unexpectedly high survival in control patients was attributed to improvements in postnatal care, which had been advancing concurrently with the evolution of the fetal interventions. After nearly 20 years of work and trials, fetal surgical interventions for CDH had failed to result in either improved survival or decreased morbidity and cannot be recommended at this time.

Postnatal Care

The push to fetal intervention was based on the conclusion by some investigators that the most affected infants are born with insufficient lung to survive. Not all researchers and clinicians accepted this premise, and the majority of research has focused on postnatal care, trying to optimize native lung function, rather than attempting to induce lung growth surgically. Exogenous surfactant, nitric oxide, high-frequency oscillatory ventilation, delayed surgery, and ECMO all have been entertained as possible keys to solve the CDH issue.

Surfactant

Early clinical evidence and data from animal models suggested that infants who have CDH are deficient in surfactant, and early case reports suggested good results with the addition of exogenous surfactant. However, evaluation of bronchoalveolar lavage fluid analyzed for components of surfactant in infants who had CDH showed no differences compared with age-matched, non-CDH controls. (12) Also, surfactant kinetic studies in infants who had CDH showed no differences in surfactant phosphatidylcholine pool size or half-life com-

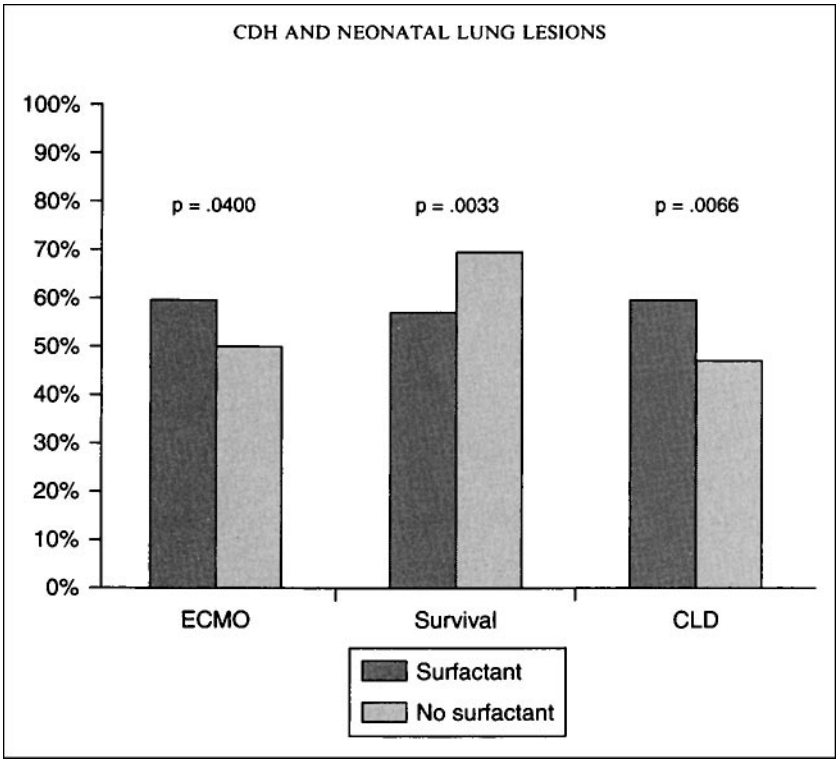

Figure 3. Comparison of use of extracorporeal membrane oxygenation (ECMO), survival, and incidence of chronic lung disease between infants who had CDH and received or did not receive surfactant. Reprinted with permission from Van Meurs et al (15).

pared with controls. (13)(14) These studies revealed no evidence of surfactant deficiency in CDH.

Evidence for clinical benefit of exogenous surfactant from larger series, provided primarily by retrospective review from the CDH Study Group, also is lacking. The CDH Study Group is a multicenter, cooperative organization of tertiary referral centers that share clinical data about CDH patients through a voluntary database. Started in 1995, this database now holds information on more than 3,000 patients. Surfactant administration and outcome in CDH patients has been reviewed retrospectively in term and preterm infants and in those who received ECMO. (15)(16)(17) Logistic regression or multivariate analyses were performed to adjust for potential differences in illness severity between those who received surfactant and those who did not.

In term infants, the use of ECMO was higher, the development of chronic lung disease was higher, and the survival rate was lower among those who received exogenous surfactant compared with those who did not (Fig. 3). Although it is impossible to eliminate the issues of illness severity and treatment bias completely in a retrospective review, the odds ratio generated after adjusted logistic regression showed no benefit to surfactant therapy with regard to survival, need for ECMO, or development of chronic lung disease. Among preterm infants, patients who received surfactant had a higher odds ratio of dying than those who did not, and multivariate analysis did not change this conclusion. Among patients who had CDH and received ECMO support, surfactant administration did not improve survival, shorten the ECMO run, or decrease the need for oxygen at 90 days. Thus, no data support the use of surfactant in newborns who have CDH.

Pulmonary Hypertension

A difficult problem in caring for infants who have CDH is pulmonary hypertension. It is important to remember that pulmonary hypertension is a clinical state, an echocardiographic finding that has many potential root causes, not all of which require specific therapy. A common mistake is to overtreat pulmonary hypertension. Pulmonary hypertension resolves in most patients over time, as long as ventilator-induced lung injury or other treatment toxicity does not intervene. Too much focus on active interventions to reduce pulmonary hypertension may do more harm than good.

Pulmonary hypertension in CDH has both a fixed and reactive component. The fixed component is due to a small pulmonary vascular bed, an effect of the pulmonary hypoplasia. Hypoplastic lungs can grow and expand, but the fixed component of pulmonary hypertension is slow to resolve, requiring weeks, months, and even years.

The reactive component of pulmonary hypertension is due to the changing resistance of the pulmonary arterioles in CDH. An increase in the reactive component of pulmonary hypertension in CDH may be due to changes in pulmonary compliance, loss of lung volume, and resultant hypoxic vasoconstriction. Maintenance of appropriate lung volume while minimizing risk of barotrauma is the most appropriate therapy. Increasing pulmonary vascular resistance also may be due to infection or to lung inflammation from ventilator-induced lung injury or it may seem to be idiopathic, worsening as a result of

unforeseen and poorly understood triggers. Regardless of the cause, pulmonary hypertension in CDH can be more severe than that seen in other forms of neonatal lung failure, such as meconium aspiration, sepsis, and primary pulmonary hypertension. It is this combination of reactive, vasoconstrictive pulmonary hypertension and fixed pulmonary hypertension from lung hypoplasia that can make medical management so difficult.

Historically, the demonstration that hyperventilation and alkalosis effectively decrease pulmonary vascular resistance and can reverse the direction of ductal shunting in neonatal pulmonary hypertension syndromes, including CDH, resulted in the rapid development of hyperventilation as standard therapy for lung failure in neonates. Because infants who have CDH often enjoy better pulmonary gas exchange in the first 24 hours after birth, only to worsen during the second 24 hours, historical management strategies quickly evolved to include preemptive hyperventilation, even in patients who had relatively mild CDH, in an attempt to prevent pulmonary hypertension from developing. It was not uncommon for ventilator settings to be pushed to attain a $Paco_2$ less than 20 mm Hg and pH greater than 7.6. All too often, ductal shunting recurred hours later, requiring further increases in ventilator settings. Once this rollercoaster of rising ventilator settings and recurrent shunting started, the end result was predictable. Lung failure inevitably occurred. Survival rates before ECMO, which evolved in large part to rescue patients from the negative effects of hyperventilation, were uniformly 50% or less in single-institution series and much less in population-based studies. Postmortem examinations of patients who succumbed to CDH showed extensive pulmonary barotrauma, as evidenced by diffuse alveolar damage, hyaline membrane formation, pneumothorax, pulmonary hemorrhage, and even interstitial fibrosis. (18)(19) Iatrogenic barotrauma represented a potentially avoidable cause of mortality in CDH patients and was estimated to contribute to 25% of CDH deaths. (19)

ECMO

ECMO evolved to rescue infants from pulmonary hypertension and ventilator-induced lung injury. Hyperventilation sometimes was profoundly successful in reversing ductal shunting and providing relief from desaturations, but at an unacceptable cost. Hyperventilation and alkalosis effectively supported many infants for several days, and corrective surgery frequently was performed in the first 24 hours. ECMO then was called upon as rescue therapy when patients developed pulmonary hypertension and lung injury after corrective surgery. Retrospective review of 730 neonates from the CDH Study Group, treated from 1995 through 1997, showed that ECMO use was associated with an improved chance of survival in those patients who had a predicted mortality of at least 80%, (20) but not in those who had less severe disease. Recently, as delayed surgery has become common, the timing of ECMO support in CDH has changed. In 1995, 20% of ECMO use in CDH patients was after repair, but by 2001, this had declined to only 5%, (21) illustrating the trend toward preoperative stabilization with ECMO, rather than postoperative rescue. By 2002, there were 2,077 patients in the CDH registry, and a total of 770 (37%) had been treated with ECMO. (21)

The decision to support with venovenous (VV) or venoarterial (VA) ECMO at most institutions is not a decision, but rather a default. Dimmitt and associates (22) reviewed the Extracorporeal Life Support Organization registry for the decade of the 1990s and reported in 2001 that VA ECMO was used in 86% of CDH patients compared with only 14% receiving VV support. The clinical status before ECMO was similar in the groups, although the VV group had received more pressors as well as 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 (12.3% versus 6.7%, $P=0.0024$) and cerebral infarction (10.5% versus 6.7%, $P=0.03$) were more common in the VA group. Sixty-four patients (17%) originally cannulated for VV ECMO were not supported sufficiently and needed conversion to VA. The survival rate for these patients was less (43.8%) than in patients originally started on VA ECMO (52%), but the difference was not statistically significant. The authors concluded that VV ECMO for CDH had similar survival rates to VA ECMO but with less neurologic morbidity and saw no disadvantage to VV ECMO as the initial mode of ECMO support in CDH. These findings mirrored those of Heiss (23) and Kugelman (24) in their single-institution reviews. The ability to predict who would later need conversion from VV to VA ECMO might be an advantage. At present, the potential neurologic advantages of VV ECMO compared with VA ECMO make it our first-choice mode of ECMO support in most patients who have CDH. However, inadequate perfusion in babies who have severe CDH on VV ECMO is not uncommon, as evidenced by rising serum lactate concentrations and rapidly declining renal function. Conversion to VA ECMO in this situation is pursued early.

Despite ongoing, widespread use of ECMO in CDH, some centers use ECMO significantly less frequently in their populations while still achieving high survival rates.

At least two centers report ECMO use in fewer than 15% of CDH patients. (25)(26) These centers exclude a small proportion of severely ill infants from ECMO who meet institutional criteria for lethal pulmonary hypoplasia, and they also have significant outborn populations. These factors could decrease the need for and use of ECMO. Nonetheless, these centers' excellent survival rates while using ECMO sparingly is highly notable.

Inhaled Nitric Oxide

The best hope of a powerful, nontoxic agent to control pulmonary hypertension in infants who have CDH has been nitric oxide. Easily delivered by inhalation directly to the lung, this powerful vasodilator was expected to have a dramatic effect on both pulmonary hypertension and survival in CDH. Although treatment with nitric oxide can have a rapid and sometimes dramatic effect on oxygenation, the effect usually is transient. Accordingly, 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. (27) This finding is in direct contrast to that reported for other forms of neonatal respiratory failure, where inhaled nitric oxide has been shown to decrease significantly the need for ECMO. (28) Nitric oxide combined with high-frequency oscillatory ventilation (HFOV) has been associated with good results in CDH, but without adequate controls. (29)(30)(31) A Cochrane review in 2001 found no clear data to support the use of inhaled nitric oxide in infants who have CDH. (32)

However, lack of documented improvement in survival does not mean that nitric oxide has no place in the care of infants who have CDH. Nitric oxide is unique in its minimal toxicity and ability to improve oxygenation quickly. Patients who have CDH can decompensate quickly, and having a tool to rescue a crashing child is valuable and probably saves neurons, even if overall survival is not affected.

Sildenafil

Sildenafil, a specific phosphodiesterase-5 inhibitor, is a more recent addition to the medical pharmacopeia for pulmonary hypertension. This agent was demonstrated to be more effective at ameliorating pulmonary hypertension in a piglet model of meconium aspiration than inhaled nitric oxide. (33) In those who had CDH, both oral (34) and intravenous (35) sildenafil have been used to treat pulmonary hypertension refractory to inhaled nitric oxide. Both of the reported patients had objective responses, but only one recovered and survived. The pattern that has emerged regarding the effects of oral and inhaled medications to treat pulmonary hypertension in CDH is that demonstration of clinical effect seldom translates into improved survival.

Gentle Ventilation

The single most significant advance in the management of CDH in the last 20 years has been the development and propagation of the neonatal ventilation strategy pioneered by Wung and associates. (36) This "gentle ventilation" strategy significantly limits inflation pressure, allows tolerance of both hypercapnia and relative postductal hypoxemia, and eliminates hyperventilation. The strategy, originally applied to non-CDH neonates who had pulmonary hypertension (36) and only later to neonates who had CDH in collaboration with Stolar (37) ran counter to conventional wisdom and was not quickly accepted into practice. (38) Most problematic, especially in the era of hyperventilation, was the concept that pulmonary vascular resistance could normalize, even without specific therapy, in the presence of hypercapnia and respiratory acidosis. However, Wilson (18) and Kays (4) validated the concept and results, demonstrating successful exportation of the treatment strategy and results. Detailed ventilation analysis of 89 patients, including 29 historical controls, showed that pneumothorax rates plummeted from 43% to 2%, and survival improved dramatically from 50% to 89% in treated patients with the introduction of a strict lung protective ventilation strategy that avoided hyperventilation and limited inflation pressures to less than or equal to 25 cm H_2O (Fig, 4). (4) The dramatic decline in pneumothorax coincided with the change in ventilatory strategy and the dramatic increase in survival. ECMO was used to support infants who had critical deficiencies of oxygen delivery. The authors concluded that the change in ventilation strategy was responsible for the dramatic increase in survival, and that most children born with CDH do indeed have enough lung to survive (Fig. 5). Others have since reported similar series with survival rates exceeding 80% in patients who have isolated CDH following change to a "gentle ventilation" strategy. (39)

It is possible to criticize the reports of improved survival with gentle ventilation as retrospective series that have few satisfactory controls. However, none of the other therapies listed have accounted for the significant change in survival attributed to the gentle ventilation strategy. High survival rates in CDH also have been reported by some investigators using HFOV, (30)(31)(40) but others report no improvement in outcome compared with the use of conventional ventilators. The improved survival with gentle ventilation and HFOV are not mu-

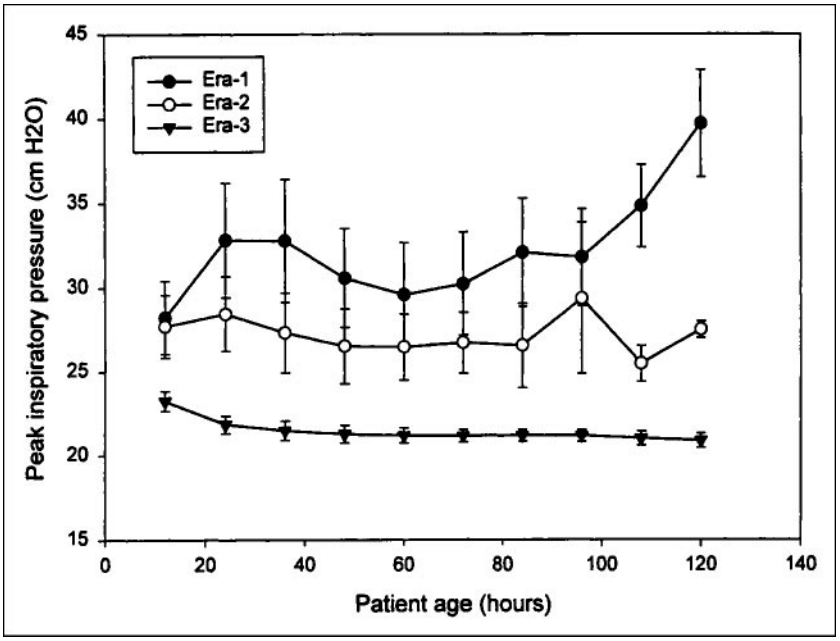

Figure 4. Peak inspiratory pressure over the first 120 hours after birth, expressed as mean ± SEM at 12-hour intervals. Significantly higher peak ventilation pressures were delivered during eras 1 and 2 compared with era 3. The differences between peak ventilation pressure varied significantly across eras, and the difference increased over time (time*era effect, P=0.00001). Era 1 (1983 to 1989)=Treatment paradigm of maximal medical therapy, including hyperventilation, Era 2 (1989 to 1992)=Treatment paradigm of maximal medical therapy, including hyperventilation, with ECMO rescue, Era 3 (1992 to 1999)=Treatment paradigm with gentle ventilation, avoiding hyperventilation and alkalosis, with ECMO rescue. Reprinted with permission from Kays et al (4).

tually exclusive, however, and the ventilation concepts central to the gentle ventilation strategy—tolerance of both hypercapnia and relative postductal hypoxemia and elimination of hyperventilation—can be applied easily to HFOV, as well. Although both expertly applied conventional mechanical ventilation and HFOV have benefits associated with their use, the important conceptual breakthrough is that ventilatory support must be as gentle and nontoxic as possible to maximize CDH survival. True understanding and application of these concepts has led to real and tangible improvements in survival at many centers across the country.

Surgical Repair

Repair of the diaphragmatic hernia defect is an important part of patient care. The primary issue at present is not whether to repair, but when. Surgical repair once was considered a life-threatening emergency, but stabilization (41) of the infant and delay of surgical repair to 24 hours and beyond has been embraced enthusiastically. Pulmonary gas exchange often improves in the first 24 hours after birth, and respiratory system compliance also improves with preoperative stabilization. Although there is no evidence that delayed repair is harmful, there is also no convincing evidence that such delay improves survival or decreases the risk of pulmonary hypertension. (42)(43)(44)(45)

Most surgeons prefer repair through an open, subcostal approach (Fig. 6). Patients who have milder CDH have enough muscle for primary repair, but those who have more severe CDH, especially with liver in the chest, do not have enough native diaphragm to close the defect. Such patients require a patch to close the defect. Requirement of patch closure is generally a marker of increased severity, and such patients also are at higher risk for gastroesophageal reflux. Because the patch material does not grow with the patient, there is a risk of future diaphragm reherniation. Recurrence of the diaphragmatic hernia generally is limited anatomically and not considered an emergency unless bowel obstruction or other secondary complication occurs. Rates of reherniation vary considerably in the literature, likely due to significant differences of technique.

Outcomes

An improved understanding of CDH pathophysiology and expanded application of lung-protective treatment strategies is resulting in an increased number of CDH survivors. Infants who survive CDH are at risk of brain injury, neurodevelopmental disability, (46) hearing loss, feeding difficulties, gastroesophageal reflux, lung disease, scoliosis, pectus excavatum, and recurrence of the diaphragmatic hernia. Some of these outcome issues are anatomic and unavoidable. Other outcome issues reflect potential toxic effects of treatment strategies and might 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

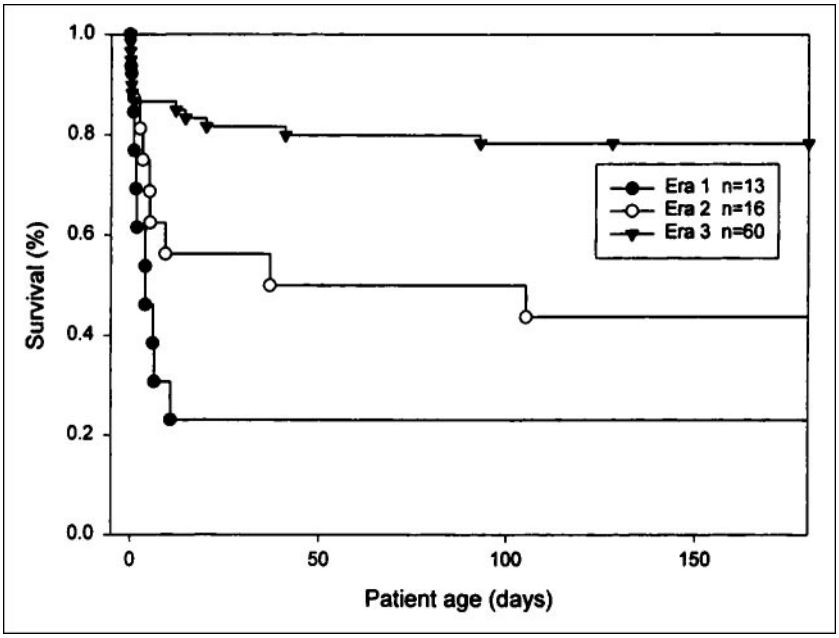

Figure 5. Life-table analysis of survival rate, all patients included, displayed over the first 180 days. Difference in the survival rate across eras is highly significant ($P<0.0001$). Era 1 (1983 to 1989)=Treatment paradigm of maximal medical therapy, including hyperventilation, Era 2 (1989 to 1992)=Treatment paradigm of maximal medical therapy, including hyperventilation, with ECMO rescue, Era 3 (1992 to 1999)=Treatment paradigm with gentle ventilation, avoiding hyperventilation and alkalosis, with ECMO rescue. Reprinted with permission from Kays et al (4).

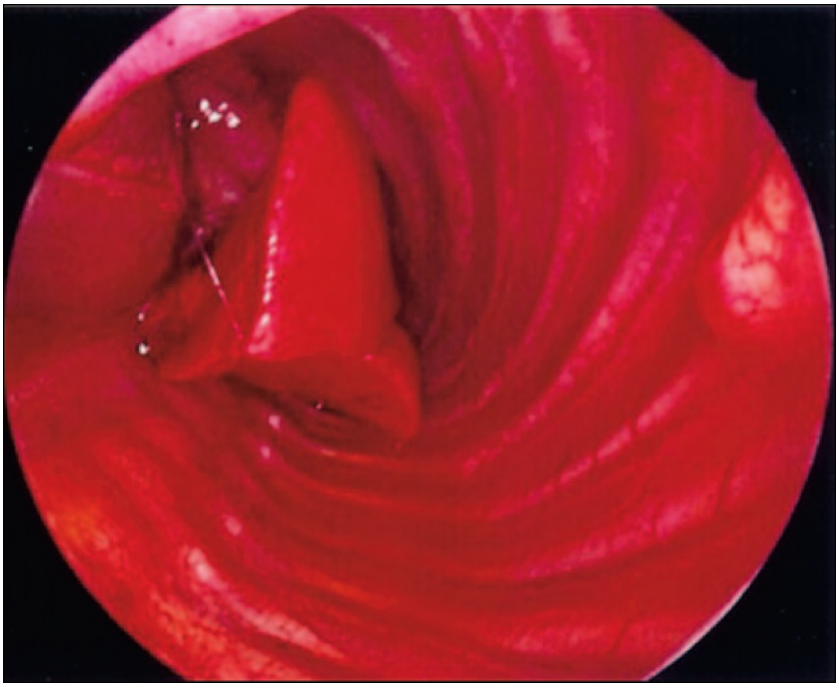

Figure 6. A view in the left thorax at repair shows a small but healthy-appearing lung.

for ECMO. Such more severely affected infants are at high risk for hypoxic-ischemic brain injury and for other secondary neurologic effects of severe illness. A review of 31 patients who had CDH and required ECMO showed that 35% had central nervous system abnormalities on computed tomography scan, manifested primarily as enlarged ventricles, focal and diffuse brain atrophy, and intracranial hemorrhage. (46) At 2 years, these patients showed mild cognitive and physical delay. In another investigation, MRI at discharge showed evidence of brain injury in eight of eight CDH survivors, some of whom had been treated for relatively mild CDH. (47) In three separate series, 44% to 55% of CDH survivors required hearing amplification due to hearing loss. (48)(49)(50) These studies are not offered necessarily as gold-standard outcomes because many of today's survivors come from the era of hyperventilation and other forms of overtreatment, but they do illustrate the high risks associated with caring for children who have CDH and that survival alone is no longer an acceptable endpoint.

Summary

CDH is a fascinating defect associated with myriad effects due to the simple lack of adequate diaphragm development. The pulmonary hypoplasia and associated difficulties in ventilation and ultimately in survival posed by this abnormality have spawned uncounted ideas of disease assessment, treatment, and outcome. Many advances through the years have improved our understanding of these facets of this birth defect, but real advances in survival have come slowly. The most successful

advance in the last 20 years has been improvement in postnatal treatment, based primarily on the understanding of the vital importance of preserving the lung parenchyma with which the child was born and the negative effects of formerly standard supportive therapies. Because of the lung preservation now achieved with gentle ventilation lung strategies, most infants affected with CDH are indeed born with sufficient lung to survive, in contrast to the opinion held by many just 15 years ago. A key component in helping children who have CDH to survive is believing that they can. Hopefully, this review and the associated references can help influence this conclusion.

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NeoReviews Quiz

11. Approximately 10% of infants born with congenital diaphragmatic hernia (CDH) have significant heart defects. Of the following, the *most* common congenital heart defect associated with CDH is:

    A. Aortic arch obstruction.
    B. Tetralogy of Fallot.
    C. Total anomalous pulmonary venous return.
    D. Transposition of the great arteries.
    E. Ventricular septal defect.

12. You are discussing with medical students the epidemiology, pathophysiology, and treatment of CDH. Of the following, the *most* accurate statement regarding CDH is that:

    A. Most cases are right-sided.
    B. Most cases occur as isolated events in nonsyndromic presentations.
    C. Most syndromic cases are associated with chromosomal translocations.
    D. Prenatal measurement of fetal lung size predicts neonatal survival reliably.
    E. Surgical occlusion of the fetal trachea improves survival in affected infants.