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Congenital Diaphragmatic Hernia: The Neonatologist's Perspective

Krisa Van Meurs, MD* and Billie Lou Short, MD†

OBJECTIVES

After completing this article, readers should be able to:

1. Delineate the studies used for prenatal diagnosis of congenital diaphragmatic hernia (CDH).
2. Describe prenatal therapies currently being investigated for the treatment of CDH.
3. Delineate the options available for ventilation of the neonate who has CDH.
4. Describe the potential complications that can be experienced by surviving infants who have CDH.

Introduction

During the past 10 years, significant changes have occurred in the diagnosis and management of congenital diaphragmatic hernia (CDH). The unsuspected birth of an infant who has CDH, the emergency transfer to a center where a pediatric surgeon and neonatologist are available, and the rush to the operating room for repair are a memory. Today we frequently provide prenatal counseling to parents of fetuses who are diagnosed as having CDH in utero, and a myriad of antenatal and postnatal therapies are available. Yet, the quest for therapeutic approaches that will optimize survival for the severely affected infant continues. Several new therapies on the horizon offer promise for the future.

Epidemiology

Most diaphragmatic hernias are posterolateral defects of the Bochdalek type, although Morgagni and pars sternalis hernias do occur. The incidence of CDH ranges from 0.08 to 0.45 per 1,000 births. The explanation for this variation in incidence most likely is underdiagnosis related to early deaths among neonates who are severely affected. Eighty-five percent of defects are left-sided,

13% are right-sided, and 2% are bilateral. Most studies have found an equal representation of genders, although a 1.25 male-to-female ratio was reported in one large population-based study (see Torfs et al in Suggested Reading).

The incidence of anomalies associated with CDH is 20% to 50%. This range is related to differences in both the definition of anomalies and in patient selection, with higher incidences reported in population-based studies (Table). CDH can be seen as an isolated defect, with multiple other anomalies, as a recognizable nonchromosomal syndrome, or as a chromosomal defect (trisomy or nontrisomy). Congenital anomalies are the most common cause of neonatal death (1.7 per 1,000 births), and CDH may account for 4% to 10% of these deaths. Survival of neonates who have CDH in centers using a wide range of therapeutic strategies ranged between 25% and 83% in the 1990s. Of interest, the survival rate varies inversely with the number of infants reported. In general, population-based studies report lower survival (43.5%) than center-based studies. This difference likely represents the "hidden mortality" of infants dying in utero or shortly after birth who never reach tertiary care centers (Fig. 1).

Prenatal Diagnosis

Both prenatal ultrasonography and measurement of maternal serum alpha-fetoprotein (MS-AFP) have

been found to be useful in identifying infants who have CDH. MS-AFP levels are obtained routinely during the 18th week of pregnancy, and low levels have been associated with CDH as well as trisomy 18 and 21. Thus, a low MS-AFP concentration should prompt additional diagnostic testing.

Ultrasonography now is considered the gold standard for diagnosing CDH antenatally. Suggestive findings include polyhydramnios, an absent or intrathoracic stomach bubble, and mediastinal and cardiac shift away from the side of the hernia. The differential diagnosis includes congenital cystic adenomatoid malformation, cystic teratoma, extrapulmonary sequestration, bronchogenic cysts, and neurogenic tumors.

Prenatal Counseling and Evaluation

Once CDH has been diagnosed antenatally by ultrasonography, it is important to determine if the defect is isolated or associated with other anomalies known to affect outcome. Level 2 ultrasonography to screen for other anatomic abnormalities should be performed, and amniocentesis should be considered to identify chromosomal abnormalities. After this evaluation, the medical team must present the various man-

ABBREVIATIONS

CDH:	congenital diaphragmatic hernia
ECMO:	extracorporeal membrane oxygenation
HFOV:	high-frequency oscillatory ventilation
iNO:	inhaled nitric oxide
ITPV:	intratracheal pulmonary ventilation
MS-AFP:	maternal serum alpha-fetoprotein
PLUG:	Plug the Lung Until it Grows
PLV:	partial liquid ventilation
SP-A:	surfactant apoprotein A

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TABLE 1. Recent Population-based Studies of Congenital Diaphragmatic Hernia (CDH)

VARIABLE	TORF ET AL	WENSTROM ET AL	STEINHORN ET AL	LANGHAM
State	California	Iowa	Minnesota	Florida
Year(s) of study	1983–1987	1983–1988	1988–1990	1988–1992
Birth population	718,208	241,473	133,162	962,516
Number of cases of CDH	237	65	48	166*
Incidence	0.33/1,000	0.27/1,000	0.36/1,000	0.17/1,000
Morgagni	5 (2%)	1 (1.5%)	0	Excluded
Other	5 (2%)	4 (6.5%)	0	Excluded
Posterolateral	227 (96%)	60 (92%)	48 (100%)	166 (100%)
Isolated	129 (54%)	47 (72%)	29 (69%)	48/59 (81%)
MCA + SYN	86 (36%)	14 (22%)	9 (21%)	9/59 (15%)
Trisomies	10 (4%)	4 (6%)	2 (5%)	1/59 (2%)
CHR	2 (5%)	0	2 (5%)	1/59 (2%)
Right:left: bilateral	27:173:5	8:47:0	6:42:1	
Prenatal diagnosis	—	12 (18%)	15 (31%)	25/58 (43%)
Mean gestational age at birth	38.0 wk	—	37±3 wk	37±4 wk
Male/female ratio	1.25	“No difference”	0.92	1.03
Birthweight (g)	2,955	—	2,726±703	2,720±865
Apgar score 1 min	—	—	4±3	—
Apgar score 5 min	—	—	5±2	—
<i>MCA + SYN = multiple anomalies and nonchromosomal syndromes; CHR = nontrisomy chromosomal defects. *Complete data available on 59 of 166 patients via questionnaire. Reprinted with permission from Langham et al. Clin Perinatol. 1996;23:671–688.</i>				

agement options to the parents, which generally include pregnancy termination or delivery at a tertiary level center that has multimodality support available. The option of pregnancy termination depends on the gestational age at the time of diagnosis. Fetal surgery now is available to selected infants diagnosed prenatally as an experimental procedure at a few research centers.

Prenatal Therapies

Several medical and surgical therapeutic options are available for the fetus diagnosed as having CDH. Studies have indicated that surfactant deficiency may contribute to the pathophysiology of CDH. Autopsy specimens from term infants who had CDH have demonstrated a decrease in the surfactant apoprotein

A (SP-A) content of alveolar type II cells. Postnatal surfactant therapy has been used in infants who had CDH, but it has not provided long-term benefit. Antenatal glucocorticoid therapy has improved pulmonary maturity and increased oxygenation and pulmonary compliance in an animal model. A multicenter randomized trial of antenatal glucocorticoid administration to mothers of infants who have CDH is needed.

In utero treatment for CDH is being studied at a small number of research centers. A prospective clinical trial of fetuses that had CDH with the liver below the diaphragm documented similarly good survival among those who underwent fetal surgery and those who received conventional treatment. Thus, the risks of fetal surgery in this population

appear to be unnecessary. Livers herniated into the chest were found to be impossible to repair in utero because of kinking of the umbilical vein.

Fetal intervention currently is focused on temporary occlusion of the fetal trachea or “PLUG” (Plug the Lung Until it Grows) for those fetuses who have CDH and liver herniation above the diaphragm. Tracheal occlusion has been shown to reverse pulmonary hypoplasia in animal models of CDH. Less invasive approaches to the fetus have evolved to include a video-fetoscopic, intrauterine technique of tracheal occlusion termed “Fetendo-PLUG” that has been associated with encouraging results. The EXIT (EX utero Intrapartum Treatment) procedure has been developed to allow for unplugging of the trachea

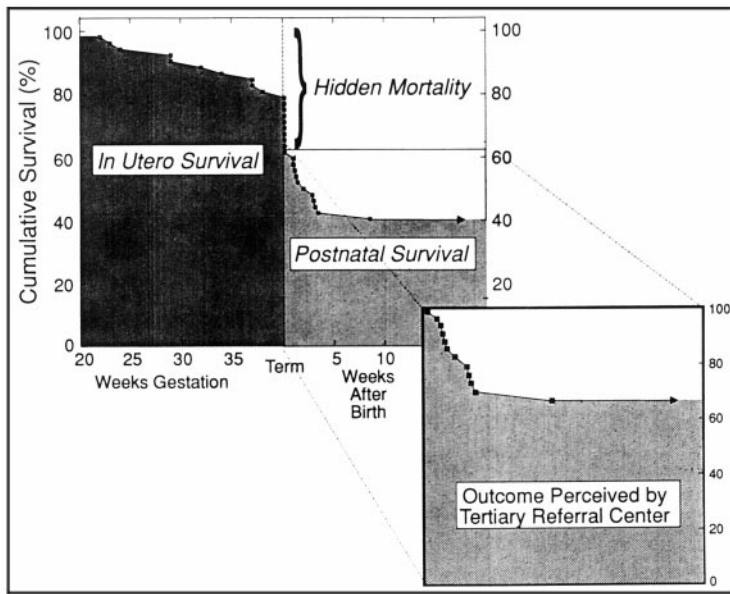


FIGURE 1. Cumulative survival plot for 83 fetuses with isolated CDH diagnosed before 24 weeks' gestation. Seven fetuses died in utero, four died soon after preterm delivery, and 16 died immediately after birth. Most of these fetuses would not be recognized as having CDH unless autopsies were performed. These deaths represent a significant hidden mortality that is not perceived when only infants seen at tertiary neonatal referral centers are considered (inset). Reprinted with permission from Harrison et al. JAMA. 1994;271:382-384.

at birth, using the placenta for support until the airway is secured.

Standard postnatal therapy, open fetal tracheal occlusion, and fetoscopic tracheal occlusion in affected fetuses who had "poor prognoses" based on liver herniation were compared recently. The diagnosis of CDH was made prior to 25 weeks' gestation, and infants had low lung-to-head ratios, a measure indicative of significant pulmonary hypoplasia

and high mortality. The survival rates were 38% in the standard therapy group, 15% in the open tracheal occlusion group, and 75% in the Fetendo-PLUG group. The number of maternal complications, such as pulmonary edema, chorioamniotic separation, premature rupture of membranes, and premature labor, appeared to be fewer in the Fetendo-PLUG group compared with the open tracheal occlusion group.

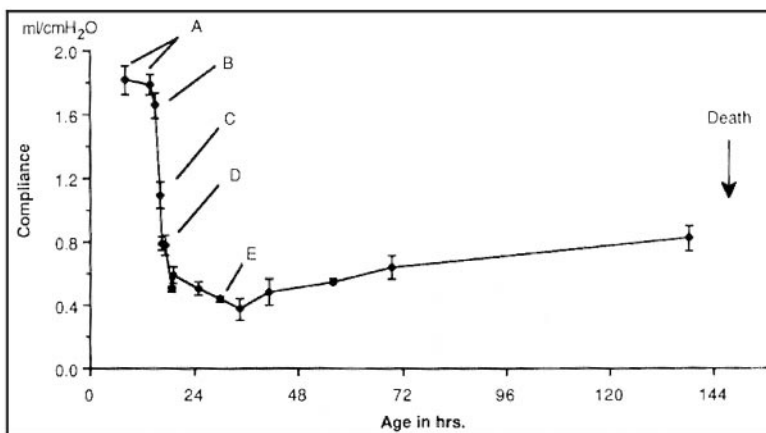


FIGURE 2. Respiratory compliance systems in one patient. Values are mean \pm SD for each series of measurements. A. Preoperative measurements; B. After induction of anesthesia; C. Immediately after closure of diaphragmatic defect; D. Immediately after suture of abdominal incision; E. Chest drain inserted on left side. Reprinted with permission from Sakai et al. J Pediatr. 1987;111:432-438.

The future of fetal surgery for CDH is yet to be determined. Its success will depend both on accurate identification of the fetus who has a poor prognosis and the demonstration of an increased survival with in utero surgery over conventional postnatal therapy for this subgroup of fetuses.

Delivery Room and Immediate Intensive Care

Antenatal diagnosis of CDH has allowed optimal immediate care of affected infants. Parents can be educated about the diagnosis and potential treatment modalities, and the delivery of medical and surgical care can be coordinated by perinatology, neonatology, and pediatric surgical services. Birth at a tertiary care center that has pediatric surgery and neonatology services as well as advanced therapies is desirable. Prompt intubation, avoidance of bag-mask ventilation, placement of a nasogastric tube to provide intestinal decompression, and ongoing care in an intensive care nursery by individuals experienced in the management of the newborn who has CDH now is the norm.

Preoperative Stabilization and Delayed Repair

Emergency surgery was the standard approach to CDH during the 1980s because it was believed that reduction of the hernia would lead to improvement in the respiratory status by allowing the lung to re-expand. With the discovery that the lung was hypoplastic, not atelectatic, and that abnormal arteriolar muscularization and resulting pulmonary hypertension were important in the pathophysiology of CDH, delayed surgical repair was introduced. Miyaska et al first reported two infants who had CDH repair delayed for 24 hours based on the rationale that the risk of pulmonary hypertension might be decreased. In 1986, Carlidge et al concluded that the use of preoperative stabilization in 17 patients was responsible for a decrease in mortality from 88% to 47%. Sakai et al demonstrated that lung compliance often deteriorates markedly after repair (Figs. 2 and

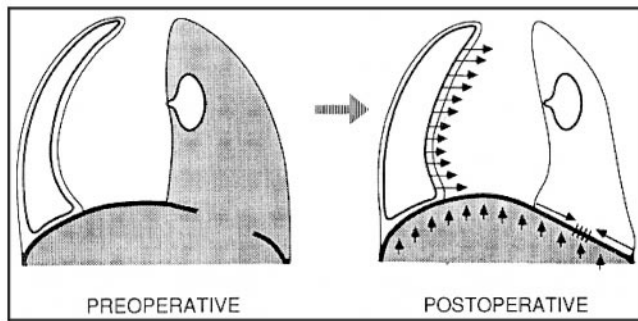


FIGURE 3. Diagram of thorax, lungs, and mediastinum in left-sided congenital diaphragmatic hernia before and after repair. Arrows represent possible changes in mechanical forces in thorax and abdomen produced by repair. Reprinted with permission from Saki et al. *J Pediatr.* 1987;111:432–438.

3). This decrease in lung compliance was attributed to changes in the mechanical forces occurring across the diaphragm after surgery. Sakai also speculated that the pulmonary vasculature may become less reactive with time if the precipitating factors for pulmonary hypertension could be avoided. Currently, most infants who have CDH are stabilized before operative intervention. The mean age at the time of surgery for infants not treated with extracorporeal membrane oxygenation (ECMO) is 73 hours (range, 0 to 443 h).

Ventilation Strategies

CONVENTIONAL MECHANICAL VENTILATION

Attempts should be made to prevent conditions known to raise pulmonary vascular resistance (hypoxemia, acidosis, hypotension, and hypercarbia). Ventilation with low peak inspiratory pressures is desirable because contralateral pneumothorax can result in added cardiorespiratory instability and decompensation. Sedation and paralysis often are employed if hypoxia persists despite other medical treatments.

HIGH-FREQUENCY OSCILLATORY VENTILATION (HFOV)

HFOV has been shown to reduce the need for ECMO in term infants who have respiratory failure. CDH has been associated with failure of HFOV and the need for ECMO

more often than other causes of neonatal respiratory failure (Fig. 4).

Paranka et al note that the severity of illness in infants who had CDH when HFOV was initiated affected the response to HFOV. The use of this therapy has continued despite no clear indication of its positive impact on survival.

Several recent articles report on the success of a multimodality approach using a combination of therapies, including delayed surgery, HFOV, inhaled nitric oxide (iNO), low ventilator pressures, permissive hypercapnea, surfactant replacement, and ECMO. These single centers cite survival rates of 80% to 90% with a multimodal approach. Multicenter studies are needed to confirm the efficacy and safety of this approach.

GENTLE VENTILATION

Wung et al first described the use of gentle ventilation in infants who had persistent pulmonary hypertension of the newborn. This therapeutic approach also has been applied in the management of infants who have CDH. It is based on the concept that overdistension of the lungs will cause pulmonary hypertension and result in lung injury due to barotrauma. The goal

is to maintain preductal saturation at greater than 90% with minimal, but adequate ventilatory support that does not involve the use of paralysis, hyperventilation, or alkalosis. $Paco_2$ levels up to 60 mm Hg are tolerated. If hypoxemia persists, tolazoline or dobutamine is added. ECMO is reserved for infants who fail this management strategy. In one comparison of survival for infants who had CDH during several time periods and employing various therapeutic strategies, the use of gentle ventilation, delayed surgery (mean age at surgery, 100 h), and no chest tube resulted in the highest survival (94%) and a low requirement for ECMO.

INTRATRACHEAL PULMONARY VENTILATION (ITPV)

ITPV has been shown to maintain low airway pressures while decreasing ventilated anatomic dead space and increasing carbon dioxide removal in animal models of severe pulmonary hypoplasia. Improvement in postductal $Paco_2$, pH, and minute ventilation has been demonstrated in a sheep model of CDH using ITPV in conjunction with a reverse thrust catheter. There is one report of ITPV use in two infants who had CDH on ECMO. Additional clinical experience will be needed before the

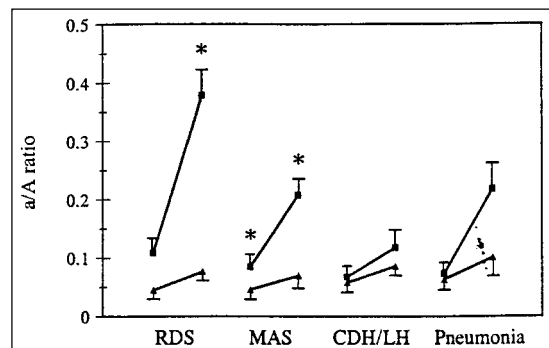


FIGURE 4. Change in the arterial-to-alveolar oxygen ratio (a/A ratio) over the first 6 hours on HFOV for four diagnostic categories. Points represent mean \pm SEM. Each line represents the change in the a/A ratio from 0 hours (just before HFOV) to 6 hours of HFOV for each group in each diagnostic category. * $P < 0.05$, HFOV responders (squares) versus nonresponders (triangles) in each diagnostic category for the indicated time point. RDS = respiratory distress syndrome; MAS = meconium aspiration syndrome; CDH/LH = congenital diaphragmatic hernia/lung hypoplasia. Reprinted with permission from Paranka et al. *Pediatrics.* 1995;95:400–404.

usefulness of this technique in infants who have CDH is determined.

ECMO

Following the successful use of ECMO in infants who had respiratory failure, its use was extended to infants who had CDH and severe hypoxemia. Conclusions about whether ECMO has resulted in increased survival for infants who have CDH vary because survival statistics are being compared across different patient populations that have inherent differences in disease severity. Some authors simply have compared survival before the use of ECMO to a subsequent time period during which ECMO was used. In one of these studies, survival during the pre-ECMO era was 47%, which was not significantly different from the 49% survival rate with ECMO. Another investigation found that the use of ECMO improved the survival rate for the “poor prognosis” infant who has CDH, as defined by Bohn et al (Table 2).

Despite the lack of conclusive evidence that ECMO improves survival, it remains a mainstay of therapy for the infant who has CDH.

The CDH Study Group found that 57% of infants reported to the CDH Registry during 1995 and 1996 received ECMO, with a survival rate of 54%.

Criteria for the selection of infants most likely to benefit from ECMO remain imprecise. It has been suggested that it is possible to avoid ECMO in those who have CDH and overwhelming pulmonary hypoplasia by requiring a preductal Pao₂ of greater than 100 torr and a Paco₂ of less than 50 torr. However, various criteria used to determine high mortality have not been able to predict survival in an ECMO-treated population, which suggests that ECMO be considered for all infants who have CDH.

Currently, ECMO is used both in the preoperative patient who fails to stabilize with medical management and in the postoperative patient who deteriorates after repair. It is clear that infants who have CDH and require ECMO preoperatively have more severe pulmonary hypoplasia and pulmonary hypertension and, thus, lower survival rates. The timing of the repair on or following ECMO remains controversial. The CDH Study Group reported that 33% of infants receiving ECMO

were repaired on bypass. The risks of operating on ECMO (bleeding) must be weighed against the risks of operative repair after ECMO decannulation (recurrence of pulmonary hypertension). Two studies have concluded that mortality and morbidity are lower if the repair is undertaken after decannulation from ECMO.

Surfactant Replacement

Respiratory failure in the infant who has CDH may be related at least partially to developmental abnormalities of the lung that result in deficiency of surfactant. Postmortem studies have shown decreased expression of SP-A most dramatically on the side of the hernia, suggesting a delay in functional maturation or development of SP-A synthesis. Amniotic fluid analysis of fetuses who have CDH have shown conflicting results. Surfactant replacement in affected infants after birth has been associated with poor results unless the surfactant is administered prior to the first breath (prophylactically) instead of as a rescue. Several authors reporting increased survival rates include surfactant treatment as part of their management strategy.

Inhaled Nitric Oxide (iNO)

iNO has been shown in several large randomized clinical trials of infants who have hypoxic respiratory failure to improve oxygenation significantly and decrease the need for ECMO. However, the response to iNO has been suggested to be disease-specific; infants who have CDH experience little improvement with iNO therapy. A later randomized clinical trial of iNO in infants who had CDH by the Neonatal iNOS Group found little improvement in oxygenation and no decrease either in the need for ECMO or in mortality (Table 3).

Lack of improvement in oxygenation with iNO use prior to ECMO or CDH repair has been documented. However, significant improvement in oxygenation may occur when iNO follows ECMO and CDH repair. In an animal model of CDH, iNO improved oxygenation

TABLE 2. Comparison of Survival Rates by Quadrant in CDH Patients Treated Conventionally (Bohn) and With ECMO (CNMC)

	Bohn survival rate*		CNMC survival rate		P
	No.	%	No.	%	
Preoperative					
Quadrant A	3/11	27	3/4	75	NS
Quadrant B	23/27	85	9/10	90	NS
Quadrant C	0/13	0	6/7	86	0.0002
Quadrant D	3/7	43	2/5	40	NS
Postoperative					
Quadrant A	4/13	30	1/1	100	NS
Quadrant B	27/27	100	9/10	90	NS
Quadrant C	0/12	0	6/9	67	0.001
Quadrant D	1/2	50	4/6	67	NS

NS, Not significant.

*Data from Bohn D, Tamura M, Perrin D, Barker G, Rabinovitch M. *J Pediatr.* 1987;111:423-431.

Reprinted with permission from Van Meurs et al. *J Pediatr.* 1990;117:954-960.

TABLE 3. Primary Outcome of CDH

	CONTROL (n = 28)	TREATMENT GROUP (INO) (n = 25)
Death ≤120 days ECMO	23 (82.1)	24 (96.0)
Died	12 (42.9)	12 (48.0)
Received ECMO	15 (53.6)*	20 (80.0)*
No. died with ECMO	4	8
No. died without ECMO	8	4
If received ECMO (±SD)		
Age initiated (days)	0.7 (0.9)	1.3 (1.9)
Hours after randomization	7.1 (6.5)	10.0 (10.5)

*Data expressed as n (%) unless otherwise indicated.
P=0.043. Reprinted with permission from NINOS. Pediatrics. 1997;97:838–845.

and decreased pulmonary artery pressure in combination with either surfactant or partial liquid ventilation. The explanation for the differences in response may reflect the inability of this therapy to act effectively if it is not delivered to the terminal lung unit. Both surfactant and partial liquid ventilation as well as administration of iNO following CDH repair and ECMO may allow iNO to be delivered to terminal lung units, thereby improving ventilation perfusion matching.

Partial Liquid Ventilation (PLV)

PLV may have an important role in the management of infants who have CDH. Perfluorocarbon is instilled

into the trachea to a physiologic functional residual capacity, and gas ventilation techniques are continued. PLV has been shown to be effective in recruiting and stabilizing noncompliant alveoli, resulting in a significantly increased Pao₂ and pulmonary compliance in infants who have CDH and are receiving ECMO. iNO has been used in conjunction with PLV in an animal model of CDH, and a significant increase in oxygenation and reduction in pulmonary hypertension over PLV alone was observed. Animal studies also have shown that lung growth was stimulated by continuous intrapulmonary distension with perfluorocarbon for a 21-day period, resulting in increased total alveolar number and total alveolar surface area (Fig. 5).

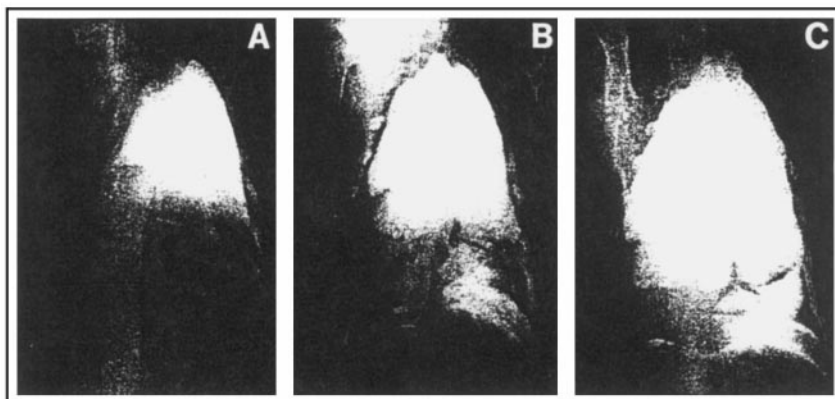


FIGURE 5. Chest radiographs of one neonatal animal after perfluorocarbon (PFC) distension, anteroposterior projection. Perflubron is radio-opaque, allowing for serial examinations of lobe volume during the study period. A. Postoperative day 1; B. Postoperative day 7; C. Postoperative day 14. Note the progressive growth of the PFC-infused lobar segment. Reprinted with permission from Nobuhara et al. J Pediatr Surg. 1998;33:292–298.

Clearly, PLV alone or in combination with other therapies offers promise for improved survival among infants who have CDH, and clinical trials are underway.

Lung Transplantation

As experience with lung transplantation in adults increased, single lung transplantation for CDH became a theoretical option. To date there has been a single case report of successful lung transplantation in a newborn who had CDH following ECMO. At the age of 5 years, the transplanted lung was removed after the side effects of immunosuppression (growth failure, infection, hirsutism, and hypertension) became increasingly problematic. Balloon occlusion of the pulmonary artery to the transplanted lung during cardiac catheterization demonstrated that pneumonectomy would be tolerated. Patient selection, donor lung size, availability, and the long-term risks of immunosuppression remain barriers to the wider use of lung transplantation in the patient who has CDH.

Outcome

SURVIVAL

Data from the CDH Study Group on 461 patients from 62 centers during 1995 and 1996 report a 63% survival for infants who have CDH. This is the best survival information on aggregate data from multiple centers and is similar to those from other similar studies. As noted previously, these data are not population-based and do not include infants dying in utero or prior to transfer to referral centers.

CDH survivors have a number of significant medical issues after hospital discharge, including chronic lung disease, gastroesophageal reflux, growth failure, reherniation, volvulus, scoliosis, sensorineural hearing loss, and developmental delay.

LUNG FUNCTION AND CHRONIC LUNG DISEASE

Studies of lung function following repair of CDH have conflicting

results. Numerous investigators have examined lung function by measuring parameters such as total lung capacity, residual volume, and vital capacity. The results have ranged from mildly reduced values to values somewhat higher than expected. The hypoplastic lung may expand to fill the hemithorax, causing the alveoli to become overdistended. Lungs grow rapidly during the first year of life, which minimizes the effect of the initial lung hypoplasia. An autopsy performed on a 5-year-old child who had CDH and died from a fall found approximately normal lung volumes, but fewer and larger alveoli in the ipsilateral lung. The contralateral lung had twice as many alveoli. In addition, fewer bronchial generations were seen in the ipsilateral lung.

Forced expiratory volume during 1 second (FEV₁) has been reported to be either normal or mildly decreased. Several authors suggested that these findings represent a pre-emphysematous state. Almost all older CDH survivors are asymptomatic, demonstrating the great reserve capacity of the lung. Whether these differences in lung function represent variations in severity between individual patients or differences in operative results is unclear. Ventilation perfusion scans performed on CDH survivors consistently have shown a persistent reduction in pulmonary blood flow to the hernia side, suggesting a primary vascular pulmonary hypoplasia.

More recent studies of infants treated with ECMO have shown that only 22% were using oxygen at discharge.

GASTROESOPHAGEAL REFLUX

Stolar et al were the first to report on anatomical and functional esophageal abnormalities in infants who survived with CDH. Seventeen of 25 (68%) infants had an air- or fluid-filled mediastinal mass confirmed by upper gastrointestinal series to be ectatic esophagus. Gastroesophageal reflux was diagnosed in 68% using pH probe studies. Many series have confirmed the high incidence of gastroesophageal reflux in those who have CDH. A history of polyhydramnios was found in many of

these infants. Foregut obstruction is associated with polyhydramnios because of interference with fetal swallowing. The potential mechanisms responsible for the development of gastroesophageal reflux include esophageal obstruction with impaired esophageal motility, shortening of the esophageal length, disruption in the angle of His by the intrathoracic position of the stomach in utero, and the complete or partial absence of the paraesophageal diaphragm. The majority of infants were treated medically, with surgical intervention required in only 9.6% to 14.8%.

FAILURE TO THRIVE

A high proportion of infants who have CDH remain below the 5th percentile for weight despite the frequent use of nasogastric and gastrostomy tube feedings. Poor growth appears to be related to gastroesophageal reflux rather than chronic lung disease.

REHERNIATION

The incidence of reherniation is increased with the use of synthetic patch repairs and ranges from 5% to 80%. The timing of the reherniation appears to vary. Symptoms occurring with reherniation are usually respiratory, such as coughing and wheezing, or feeding difficulties.

VOLVULUS

Patients who have CDH have malrotation, and a small number will have obstruction of the small bowel due to midgut volvulus or adhesions. If unrecognized, this complication can be life-threatening.

SCOLIOSIS

Chest wall and spinal deformities are found in children and adults who have CDH. A study of 60 adult CDH survivors (mean age, 29 y) documented chest asymmetry in 48%, pectus excavatum in 18%, and significant scoliosis with a Cobb angle of at least 10 degrees in 27%. The incidence of these abnormalities was greatest among those who had a large diaphragmatic defect and those who had undergone thoracotomy versus laparotomy. It is likely that repair of a large defect causes tension, which may interfere with nor-

mal development of the thoracic cage and promote asymmetry. Other authors have noted lower incidences of chest wall and spinal deformities, but these reports have had shorter periods of follow-up. Clearly, CDH survivors should be monitored for these abnormalities.

HEARING LOSS

Risk factors for hearing impairment in the newborn population include low birthweight, use of ototoxic medications such as aminoglycosides and furosemide, hyperbilirubinemia, congenital infections, meningitis, and hyperventilation. Hyperventilation with the induction of a respiratory alkalosis has been associated with the development of a progressive high-frequency sensorineural hearing loss. One study documented hearing loss in 52.5% of infants who had persistent pulmonary hypertension that was associated with exposure to high pH levels and long periods of ventilation. The reported incidence of hearing loss in ECMO survivors has ranged from 4% to 28%. A recent study of hearing in CDH survivors treated with and without ECMO found almost 60% to have sensorineural hearing loss. This hearing loss is progressive, and normal results on a hearing screen at discharge do not preclude the development of later hearing loss. Regular hearing screening is a necessity for CDH survivors.

DEVELOPMENTAL OUTCOME

Limited information is available about the long-term neurodevelopmental outcome of CDH survivors. In general, reports have focused on the outcome of those treated with ECMO. In one group of ECMO-treated CDH survivors between the ages of 8 months and 5 years, 47% of infants had normal scores on Bayley Scales or Stanford-Binet; none scored below 70. Seventeen of 18 children had abnormalities on neuroimaging, but only three had major abnormalities. None had seizure disorders requiring ongoing treatment. The authors concluded that the neurodevelopmental outcome for infants who have CDH is not dissimilar from that of other children treated with ECMO.

Another report of 14 CDH survivors during the first year of life showed lower Bayley scores and a higher incidence of hypotonia when compared with other ECMO survivors. Infants who have CDH have been shown in numerous studies to have longer periods of hospitalization and higher rates of chronic lung disease, both of which affect development. Longer term follow-up of larger groups of ECMO- and nonECMO-treated CDH survivors is needed.

Summary

Despite several decades of investigation and a vast array of new therapeutic approaches, the optimal therapeutic strategy for the newborn who has CDH remains undetermined. Ongoing data collection and the development of multicenter clinical trials should clarify which therapies are most likely to be of benefit.

SUGGESTED READING

- Adolph V, Flageole H, Perreault T, et al. Repair of congenital diaphragmatic hernia after weaning from extracorporeal membrane oxygenation. *J Pediatr Surg.* 1995; 30:349–352
- Asabe K, Tsuji K, Handa N, et al. Immunohistochemical distribution of surfactant apoprotein-A in congenital diaphragmatic hernia. *J Pediatr Surg.* 1997;32:667
- Atkinson JB, Poon MW. ECMO and the management of congenital diaphragmatic hernia with large diaphragmatic defects requiring a prosthetic patch. *J Pediatr Surg.* 1992;27:754–756
- Bernbaum J, Schwartz IP, Gerdes M, D'Agostino JA, Coburn CE, Polin RA. Survivors of extracorporeal membrane oxygenation at 1 year of age: the relationship of primary diagnosis with health and neurodevelopmental sequelae. *Pediatrics.* 1995;96:907–913
- Bohn D, Tamura M, Perrin D, Barker G, Rabinovitch M. Ventilatory predictors of pulmonary hypoplasia in congenital diaphragmatic hernia, confirmed by morphologic assessment. *J Pediatr.* 1987;111: 423–431
- Cartlidge PHT, Mann NP, Kapila L. Preoperative stabilization in congenital diaphragmatic hernia. *Arch Dis Child.* 1986;61: 1226–1228
- Chatrath RR, El Shafie M, Jones RS. Fate of hypoplastic lungs after repair of congenital diaphragmatic hernia. *Arch Dis Child.* 1971;46:633–635
- Clark RH, Hardin WD Jr, Hirschl RB, et al. Current surgical management of congenital diaphragmatic hernia: a report from the Congenital Diaphragmatic Hernia Study Group. *J Pediatr Surg.* 1998;33: 1004–1009
- Cornish JD, Gerstmann DR, Clark RH, et al. Extracorporeal membrane oxygenation and high-frequency ventilation; potential therapeutic relationships. *Crit Care Med.* 1987; 15:831–834
- D'Agostino JA, Bernbaum JC, Gerdes M, et al. Outcome for infants with congenital diaphragmatic hernia: the first year. *J Pediatr Surg.* 1995;30:10–15
- DeAnda A, Cahill JL, Bernstein D, Starnes VA, Reitz BA. Elective transplant pneumectomy. *J Pediatr Surg.* 1998;33: 655–656
- Dillon PW, Cilley RE, Hudome SM, Ozkan EN, Krummel TM. Nitric oxide reversal of recurrent pulmonary hypertension and respiratory failure in an infant with CDH after successful ECMO therapy. *J Pediatr Surg.* 1995;30:743–744
- Finer NN, Tierney A, Etches PC, Peliowski A, Ainsworth W. Congenital diaphragmatic hernia: developing a protocolized approach. *J Pediatr Surg.* 1998;33: 1331–1337
- Freckner B, Ehren H, Granholm T, Linden V, Palmer K. Improved results in patients who have congenital diaphragmatic hernia using preoperative stabilization, extracorporeal membrane oxygenation and delayed surgery. *J Pediatr Surg.* 1997;32: 1185–1189
- French Paediatric Study Group of Inhaled NO. Disease-related response to inhaled nitric oxide in newborns with severe hypoxaemic respiratory failure. *Eur J Pediatr.* 1998;157:747–752
- Freyschuss U, Lannergren K, Freckner B. Lung function after repair of congenital diaphragmatic hernia. *Acta Paediatr Scand.* 1984;73:589–593
- Glick PL, Leach CL, Besner GE, et al. Pathophysiology of congenital diaphragmatic hernia: III. Exogenous surfactant therapy for the high risk neonate with CDH. *J Pediatr Surg.* 1992;27:866–869
- Harrison MR, Adzick NS, Bullard KM, et al. Correction of congenital diaphragmatic hernia in utero: VII. A prospective trial. *J Pediatr Surg.* 1997;32:1637–1642
- Harrison MR, Adzick NS, Estes JM, et al. A prospective study of the outcome for fetuses with diaphragmatic hernia. *JAMA.* 1994;271:382–384
- Harrison MR, Adzick NS, Flake AW. Correction of congenital diaphragmatic hernia in utero: VI. Hard earned lessons. *J Pediatr Surg.* 1993;28:1411–1418
- Harrison MR, Adzick NS, Longaker MT, et al. Successful repair in utero of a fetal diaphragmatic hernia after removal of herniated viscera from the left thorax. *N Engl J Med.* 1990;322:1582–1584
- Harrison MR, Mychaliska GB, Albanese CT, et al. Correction of congenital diaphragmatic hernia in utero: IX. Fetuses with poor prognosis (liver herniation and low lung-to-head ratio) can be saved by fetoscopic temporary tracheal occlusion. *J Pediatr Surg.* 1998;33:1017–1023
- Heiss K, Manning P, Oldham KT, et al. Reversal of mortality for congenital diaphragmatic hernia with ECMO. *Ann Surg.* 1989;209:225–230
- Henricks-Munoz KD, Walton JP. Hearing loss in infants with persistent fetal circulation. *Pediatrics.* 1988;81:650–656
- Hisanga S, Shimokawa H, Kashiwawara Y, et al. Unexpectedly low lecithin/sphingomyelin ratio associated with fetal diaphragmatic hernia. *Am J Obstet Gynecol.* 1984; 149:905–906
- Jeandot R, Lambert B, Brendel AJ, Guyot M, Demarquez JL. Lung ventilation and perfusion scintigraphy in the follow up of repaired congenital diaphragmatic hernia. *Eur J Nucl Med.* 1989;15:591–596
- Karamanoukian HL, Glick PL, Wilcox DT, Rossman J, Holm BA, Morin FC. Pathophysiology of congenital diaphragmatic hernia: VIII. Inhaled nitric oxide requires exogenous surfactant therapy. *J Pediatr Surg.* 1995;30:1–4
- Karamanoukian HL, Glick PL, Zayek M, et al. Inhaled nitric oxide in congenital hypoplasia of the lungs due to diaphragmatic hernia or oligohydramnios. *Pediatrics.* 1994;94:715–718
- Kieffer J, Sapin E, Berg A, et al. Gastroesophageal reflux after repair of congenital diaphragmatic hernia. *J Pediatr Surg.* 1995;30:1330–1333
- Koot VCM, Bergmeijer JH, Bos AP, Molenaar JC. Incidence and management of gastroesophageal reflux after repair of congenital diaphragmatic hernia. *J Pediatr Surg.* 1993;28:48–52
- Landau LI, Phelan PD, Gillam GL, Coombs E, Noblett HR. Respiratory function after repair of congenital diaphragmatic hernia. *Arch Dis Child.* 1977;52:282–286
- Langham MR, Kays DW, Ledbetter CJ, Frentzen B, Sanford LL, Richards DS. Congenital diaphragmatic hernia: epidemiology and outcome. *Clin Perinatol.* 1996; 23:671–688
- Lasky RE, Wiorek L, Becker TR. Hearing loss in survivors of neonatal extracorporeal membrane oxygenation and high-frequency oscillatory therapy. *J Am Acad Audio.* 1998;9:47–58
- Lotze A, Knight GR, Anderson KD, et al. Surfactant (Beractant) therapy for infants with congenital diaphragmatic hernia on ECMO. Evidence of persistent surfactant deficiency. *J Pediatr Surg.* 1994;29: 407–412
- Lund DP, Mitchell J, Kharasch V, et al. Congenital diaphragmatic hernia: the hidden morbidity. *J Pediatr Surg.* 1994;29: 186–191
- Miyaska K, Sandawa H, Hakano T, et al. Congenital diaphragmatic hernia: is emergency radical surgery really necessary? *Jpn J Pediatr Surg.* 1984;16:1417–1423
- Mychaliska GB, Bealer JF, Graf JL, et al. Operating on placental support: the Ex Utero Intrapartum Treatment (EXIT) procedure. *J Pediatr Surg.* 1996;32:227–231
- Nagaya M, Akatsuka H, Kato J. Gastroesophageal reflux occurring after repair of congenital diaphragmatic hernia. *J Pediatr Surg.* 1994;29:1447–1451
- Newman KD, Anderson KD, Van Meurs K, Parson S, Loe W, Short B. Extracorporeal membrane oxygenation and congenital diaphragmatic hernia: should any infant be

- excluded? *J Pediatr Surg.* 1990;25:1048–1053
- Nobuhara KK, Fauza DO, DiFiore JW, et al. Continuous intrapulmonary distension with perfluorocarbon accelerates neonatal (but not adult) lung growth. *J Pediatr Surg.* 1998;33:292–298
- Nobuhara KK, Lund DP, Mitchell J, Kharsch V, Wilson JM. Long-term outlook for survivors of congenital diaphragmatic hernia. *Clin Perinatol.* 1996;23:873–887
- O'Rourke PP, Lillehei CW, Crone PK, Vacanti JP. The effect of extracorporeal membrane oxygenation on the survival of neonates with high-risk congenital diaphragmatic hernia: 45 cases from a single institution. *J Pediatr Surg.* 1991;26:147–152
- O'Toole SJ, Karamanoukian HL, Sharma A, et al. Surfactant rescue in the fetal lamb model of congenital diaphragmatic hernia. *J Pediatr Surg.* 1996;31:1105–1109
- Paranka MS, Clark RH, Yoder BA, Null DM. Predictors of failure of high-frequency ventilation in term infants with severe respiratory failure. *Pediatrics.* 1995;95:400–404
- Pranikoff T, Gauger PG, Hirschl RB. Partial liquid ventilation in newborn patients with congenital diaphragmatic hernia. *J Pediatr Surg.* 1996;31:613–618
- Reickert CA, Hirschl RB, Atkinson JB, et al. Congenital diaphragmatic hernia survival and use of extracorporeal life support at selected level III nurseries with multimodality support. *Surgery.* 1998;123:305–310
- Reid IS, Hutcherson RJ. Long-term follow-up of patients with congenital diaphragmatic hernia. *J Pediatr Surg.* 1976;11:939–942
- Reyes C, Chang LK, Waffarn F, Mir H, Wardeh MJ, Sills J. Delayed repair of congenital diaphragmatic hernia with early high-frequency oscillatory ventilation during preoperative stabilization. *J Pediatr Surg.* 1998;33:1010–1016
- Roberts JD, Fineman JR, Morin FC, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. *N Engl J Med.* 1997;336:605–610
- Robertson CM, Cheung PY, Haluschak MM, Elliott CA, Leonard NJ. High prevalence of sensorineural hearing loss among survivors of neonatal congenital diaphragmatic hernia. *Am J Otolaryngol.* 1998;19:730–736
- Sakai H, Tamura M, Hosokawa Y, Bryan AC, Barker GA, Bohn DJ. Effect of surgical repair on respiratory mechanics in congenital diaphragmatic hernia. *J Pediatr.* 1987;111:432–438
- Schnitzer JJ, Hedrick HL, Pacheco BA, et al. Prenatal glucocorticoid therapy reverses pulmonary immaturity in congenital diaphragmatic hernia in fetal sheep. *Ann Surg.* 1996;224:430–439
- Schnitzer JJ, Thompson JE, Hedrick HL. A new ventilator improves CO₂ removal in newborn lambs with congenital diaphragmatic hernia. *Crit Care Med.* 1999;27:109–112
- Sigalet DL, Tierney A, Adolph V, et al. Timing of repair of congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation support. *J Pediatr Surg.* 1995;30:1183–1187
- Stolar C, Dillon P, Reyes C. Selective use of extracorporeal membrane oxygenation in the management of congenital diaphragmatic hernia. *J Pediatr Surg.* 1988;23:207–211
- Stolar CJH, Levy JP, Dillon PW, Reyes C, Belamarich P, Berdon WE. Anatomic and functional abnormalities of the esophagus in infants surviving congenital diaphragmatic hernia. *Am J Surg.* 1990;159:204–207
- Sullivan KM, Hawgood S, Flake AW, Harrison MR, Adzick NS. Amniotic fluid phospholipid analysis in the fetus with congenital diaphragmatic hernia. *J Pediatr Surg.* 1994;29:1020–1024
- The Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med.* 1997;336:597–604
- The Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. *Pediatrics.* 1997;97:838–845
- Thurlbeck WM, Kida K, Langston C, et al. Postnatal lung growth after repair of diaphragmatic hernia. *Thorax.* 1979;34:338–343
- Torfs CP, Curry CJR, Bateson TF, et al. A population-based study of congenital diaphragmatic hernia. *Teratology.* 1992;46:555–565
- Vanamo K, Peltonen J, Rintala R, Lindahl H, Jaaskelainen, Louhimo I. Chest wall and spinal deformities in adults with congenital diaphragmatic defects. *J Pediatr Surg.* 1996;31:851–854
- Vanamo K, Rintala RJ, Lindahl H, Louhimo I. Long-term gastrointestinal morbidity in patients with congenital diaphragmatic defects. *J Pediatr Surg.* 1996;31:551–554
- VanderWall KJ, Skarsgard ED, Filly RA, Eckert J, Harrison MR. Fetendo-Clip. A fetal endoscopic tracheal clip procedure in a human fetus. *J Pediatr Surg.* 1997;32:970–972
- Van Meurs KP, Newman KD, Anderson KD, Short BL. Effect of extracorporeal membrane oxygenation on survival of infants with congenital diaphragmatic hernia. *J Pediatr.* 1990;117:954–960
- Van Meurs KP, Rhine WD, Benitz WE, et al. Lobar lung transplantation as a treatment for congenital diaphragmatic hernia. *J Pediatr Surg.* 1994;29:1557–1560
- Van Meurs KP, Robbins ST, Reed VL, et al. Congenital diaphragmatic hernia: long-term outcome in neonates treated with extracorporeal membrane oxygenation. *J Pediatr.* 1993;122:893–899
- Wilson JM, Thompson JR, Schnitzer JJ, et al. Intratracheal pulmonary ventilation and congenital diaphragmatic hernia: a report of two cases. *J Pediatr Surg.* 1993;28:484–487
- Wilcox DT, Glick PL, Karamanoukian HL, Leach C, Morin FC, Fuhrman BP. Perfluorocarbon-associated gas exchange improves pulmonary mechanics, oxygenation, ventilation, and allows nitric oxide delivery in the hypoplastic lung congenital diaphragmatic hernia lamb model. *Crit Care Med.* 1995;23:1858–1863
- Wung JT, James LS, Kilchevsky E, et al. Management of infants with severe respiratory failure and persistence of the fetal circulation without hyperventilation. *Pediatrics.* 1985;76:488–494
- Wung JT, Sahni R, Moffitt ST, Lipsitz E, Stolar CJH. Congenital diaphragmatic hernia: survival with very delayed surgery, spontaneous respiration and no chest tube. *J Pediatr Surg.* 1995;30:406–409

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