Short-Term Outcomes and Medical and Surgical Interventions in Infants with Congenital Diaphragmatic Hernia

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Abstract

Objective The aim of this study is to characterize medical and surgical therapies and short-term outcomes in infants with congenital diaphragmatic hernia (CDH).

Study Design Retrospective analysis of CDH infants admitted to 27 children's hospitals submitting data to Children's Hospital Neonatal Database (CHND) from 2010 to 2013, stratified by gestational age, birth weight, and survival.

Results A total of 572 infants were identified, 508 (89%) born $\geq$ 34 weeks' gestation and $\geq$ 2 kg. More mature infants had higher APGAR scores, shorter duration of mechanical ventilation, and were more likely to receive extracorporeal membrane oxygenation (ECMO). Overall, mortality for the cohort was 29%, with mortality lower in infants born $\geq$ 34 weeks' gestation and $\geq$ 2 kg (26 vs. 50%, $p < 0.01$). Nonsurvivors were more likely to receive treatment with high-frequency oscillatory ventilation (HFOV), vasopressors, pulmonary vasodilators, and ECMO, and to have associated major congenital anomalies than survivors. In hospital morbidity and complications were relatively uncommon among survivors.

Conclusion Infants with CDH have a high risk of morbidity and mortality, and for preterm infants with CDH those risks are amplified. Patterns of respiratory and circulatory support appeared to be different for survivors. In addition to established data registries, this consortium of regional neonatal intensive care units provides a new collaborative effort to describe short-term outcomes for infants referred with CDH.

Keywords
- congenital diaphragmatic hernia
- neonatal
- pulmonary hypertension
- prematurity
- NICU
- pulmonary hypoplasia
- respiratory failure

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Congenital diaphragmatic hernia (CDH) is a life-threatening anomaly occurring in 1 of every 3,000 to 5,000 live births. It is associated with respiratory failure, pulmonary hypoplasia, pulmonary hypertension, and mortality ranging from 24 to 40%.[1–4] International groups have studied these infants from both a medical and surgical perspective,[5,6] and many short-term outcomes have been previously defined.[7] Although some risk factors for mortality have been described,[8] early prediction of mortality and other morbidities remains a challenge.[9–11]

Most neonatal intensive care units (NICUs) have few patients with CDH.[12,13] Even in the regional NICU that cares for infants referred with CDH, patient accrual is insufficient to adequately describe patient characteristics, the distribution of applied therapies, or short-term outcomes over a contemporary period.[14] Longitudinal single-center reports are difficult to interpret as institutional practice and technologic advances vary over time, making the use of historic controls fraught with bias. Detailed description of infants with CDH in a contemporary, multi-institutional cohort is a necessary step to associate risk factors with patient outcomes. Moreover, a traditional focus on the surgical procedures has left the exploration of the risks and benefits of the applied medical therapies less well defined.

Using an extensive clinical data set of infants referred to participating regional NICUs, we focused this report on the characterization of infants with CDH and their in-hospital outcomes for a large, multicenter contemporary cohort in the United States. Because infants born less than 34 weeks' gestation have a higher risk or mortality and are typically not considered candidates for therapies such as extracorporeal membrane oxygenation (ECMO), we stratified the analysis of medical and surgical inventions and outcomes by gestational age (GA) and birth weight (BW).

Patients and Methods

The Children's Hospital Neonatal Database (CHND) captures clinical data on all infants admitted to 27 participating regional NICUs.[13] For this study, all infants with a diagnosis of CDH over a 4-year period (2010–2013) were identified. Infants who had surgical repair before referral or had previously been discharged home were not included in this analysis. The cohort included patients from 22 of 27 hospitals who contributed expanded data focused on CDH patients; thus, patients from the remaining five hospitals that did not participate in the CDH module were prospectively excluded ($n = 49$). Chart abstractors at each site completed prospective training including review of clinical definitions, participation in web-based seminar tutorials, and case-based practice.[13] The Stanley Manne Children's Research Institute's Institutional Review Board (Chicago, Illinois) approved this analysis (#2011–14673), and each participating site has ongoing local institutional review board approval for participation in the data registry.

Eligible infants were described using maternal and infant demographic, birth, and clinical characteristics including selected variables that occurred before referral to the regional NICU. These were reported for the whole cohort and after stratification: those born < 34 weeks' gestation or < 2 kg (cohort 1) and those born ≥ 34 weeks' gestation and ≥ 2 kg (cohort 2). These groups were chosen to isolate the larger, more mature infants who may have been eligible candidates to receive ECMO.[15]

The characteristics of the type of defect, type of repair, surgical approach, and distribution of selected perioperative sequelae were reported. Clinical interventions provided were described, including respiratory and vasopressor support, and receipt of ECMO or pulmonary vasodilator medications. For these variables, the cohort was stratified by mortality to demonstrate the unadjusted differences in the receipt of therapies.

The outcomes described are those achieved before hospital discharge from the regional NICU. Some infants were transferred to another institution, and data on the final disposition of these infants were not measured systematically. The prevalence of other selected morbidities including the prevalence of central line associated blood stream infections, duration of mechanical ventilation, and hospital length of stay (LOS) are reported for the duration of stay within the participating CHND hospitals.

Data description and analyses were performed with SAS v9.3 (Cary, NC). Student *t*-test, chi-squared, and bivariable analyses were applied, as appropriate. Nonparametric testing was applied when the distribution of selected measures did not conform to a normal distribution.

Results

Of the 49,403 records in CHND, 642 infants (1.4%) had a diagnosis of CDH for their first admission to these participating regional NICUs. After excluding infants with incomplete data ($n = 49$) and those who were repaired ($n = 3$) or previously home before referral ($n = 18$), 572 infants with CDH were eligible for analysis. Patient volume varied by center (median, 23 patients per center; [inter-quartile range, IQR, 10, 34]), and six centers had more than 36 CDH patients included.

Prenatal and Perinatal Characteristics

Prenatal diagnosis was made in 64% of CDH patients, and most infants (89%) were born ≥ 34 weeks' gestation and ≥ 2 kg (cohort 2). Small for GA,[16] multiple gestation, cesarean delivery, antenatal steroid administration, APGAR scores ≤ 5 at 1, 5, or 10 minutes, and exogenous surfactant therapy before referral were more frequently observed in cohort 1 compared with those in cohort 2 (►**Table 1**). Infants were referred early after birth (median, 3.6 hours; IQR, 1.5, 6.3 hours) and 89% were referred before 24 hours of age. Only one infant at any gestation had confirmed sepsis present at the time of referral.

Congenital Diaphragmatic Hernia Defect and Operative Repair

Characteristics of the diaphragmatic hernia itself were recorded among those who were surgically repaired ($n = 450$; 78.6% of CDH patients). Right-sided defects were more

Table 1 Demographic variables associated with CDH patients referred to CHND NICUs

Variable	All	GA/BW stratification		*p* Value
		< 34 wks or < 2 kg	≥ 34 wks and > 2 kg	
Number of CDH patients	572	64 (11)	508 (89)	
Median GA in weeks (IQR)	38 (36, 39)	32 (31, 33)	38 (37, 39)	< 0.001
Median BW in grams (IQR)	3,000 (2,580, 3,345)	1,777 (1,438, 1,970)	3,068 (2,745, 3,400)	< 0.001
SGA (< 10%ile)	68 (12)	14 (22)	54 (11)	0.014
Multiple gestations	23 (4)	8 (13)	15 (3)	0.002
Cesarean delivery	256 (45)	42 (66)	214 (42)	0.001
Antenatal steroids	65 (11)	26 (41)	39 (8)	< 0.001
APGAR @1 minute ≤ 5	333 (58)	47 (73)	286 (56)	0.004
APGAR @5 minute ≤ 5	142 (25)	26 (41)	116 (23)	0.007
APGAR @10 minute ≤ 5	55 (10)	11 (17)	44 (9)	0.005
Surfactant before referral	90 (16)	33 (52)	57 (11)	< 0.001

Abbreviations: BW, birth weight; CDH, congenital diaphragmatic hernia; GA, gestational age; IQR, interquartile range; SGA, small for gestational age.
Note: Using published gender-specific and gestational age-specific normative values.[8] Data presented are *N* (%) or median (IQR).

common in cohort 1 (28.2 vs. 14.8%, $p = 0.028$) as was liver herniation into the thorax (61.5 vs. 47.5%, $p = 0.002$). In contrast, thoracostomy tubes were more frequently placed in the larger, more mature infants (45.5 vs. 28.2%; $p = 0.043$), although most were on the side ipsilateral to the defect and placed after CDH repair (84%). In both the strata, the majority of infants received surgical repair in the first (49%) or second (26%) weeks of life, with a median age at repair of 7 days (IQR = 3, 13). Most operative repairs occurred in the operating room (62%) rather than in the NICU (38%). Patch (51%) and primary (47%) repairs were divided equally among infants, and were similar in frequency in both strata ($p = 0.66$). Patch repair was associated with an increased risk for mortality relative to primary repair (12 vs. 1.3%, $p < 0.01$) as was need for thoracostomy tube on either the ipsilateral or contralateral side before surgical repair ($p < 0.0001$). Of those infants who were surgically repaired, 11% ($n = 52$) received an operative repair while receiving ECMO. Complications after operative repair were infrequent with postoperative chylothorax (6.4%), liver/splenic laceration (2.9%), and recurrent hernia before discharge (2.4%) noted as the three most common problems. Infections, postoperative hemorrhage, intestinal ischemia/injury, and abdominal compartment syndrome were reported as singular events in the entire cohort. Complications were similar by GA and BW strata.

Medical Therapies Provided during Hospitalization

CDH infants received complex medical support during their NICU hospitalization (►**Table 2**). Infants were typically intubated on their day of birth (94%), and both mechanical ventilation and noninvasive respiratory supports were nearly universally applied with few differences between the GA/BW strata. Infants in cohort 1 were treated less commonly with conventional mechanical ventilation than those in cohort 2, although use of high-frequency oscillatory ventilation (HFOV) was similar between the groups. For those infants receiving mechanical ventilation, the total duration of respiratory support was longer in the preterm cohort. Not surprisingly, preterm infants were less likely to receive ECMO, but for those treated, the median duration of ECMO therapy was significantly longer (cohort 1: 19 days vs. cohort 2: 11 days; $p = 0.04$), and survival after ECMO trended lower (cohort 1 = 17 vs. cohort 2 = 52%; $p = 0.11$). Vasopressors and pulmonary vasodilator medications were frequently used; of note, inhaled nitric oxide was used in the majority (62%) of infants and 22% received sildenafil.

Mortality

Overall mortality was 29%; preterm infants had a mortality rate of 50%, compared with 27% for infants in cohort 2 ($p < 0.001$) (►**Table 3**). Prenatal diagnosis of CDH was more frequently made in nonsurviving infants (77 vs. 59%; $p < 0.001$). Mortality associated with ECMO use was 49% compared with 20% in those who did not receive ECMO ($p < 0.001$). Nonsurviving infants were less likely to receive conventional mechanical ventilation, and more likely to be treated with high-frequency mechanical ventilation (►**Table 4**). Only seven infants in the entire cohort did not receive mechanical ventilation outside the immediate perioperative period, and one was a nonsurvivor. Vasopressor and prostanoid medications as well as ECMO were used more frequently among nonsurvivors, and the median duration of ECMO was longer than in survivors (14.3 vs. 8.6 days, $p < 0.001$). Associated major congenital anomalies (cardiac, genetic syndrome, and other major anomalies) were more frequent in nonsurviving infants (41 vs. 27%; $p = 0.008$). The recorded causes of death were related to pulmonary hypoplasia, pulmonary hypertension, and/or cardiopulmonary failure in all but 10 patients. For these 10 patients, their cause of death was related to hemorrhage ($n = 2$), brain injury ($n = 6$), vascular dissection ($n = 1$), and thrombosis ($n = 1$).

Table 2 Respiratory support during CDH hospitalization, stratified by gestational age and birth weight

VARIABLE	ALL, ($N = 572$)	< 34 wks or < 2 kg ($n = 64$)	≥ 34 wks and > 2 kg ($n = 508$)	p Value
Advanced respiratory support				
Median days on respiratory support (median, IQR)	18 (10, 38)	46 (13, 74)	18 (10, 36)	0.039
Median days on mechanical ventilation	15 (6, 29)	17 (5, 38)	15 (6, 28)	0.735
High-frequency oscillatory ventilation, *N* (%)	225 (39)	23 (36)	202 (40)	0.590
Median duration in days	5 (2, 13)	7 (2, 19)	5 (2, 13)	0.214
Conventional ventilation	510 (89)	50 (78)	460 (91)	0.005
Median duration in days	12 (5, 23)	14 (3, 47)	12 (5, 22)	0.366
Vasopressors				
Dopamine	419 (73)	50 (78)	369 (73)	0.454
Epinephrine	192 (34)	23 (36)	169 (33)	0.675
Milrinone	172 (30)	17 (27)	155 (31)	0.565
Dobutamine	76 (13)	12 (19)	64 (13)	0.173
Vasopressin	30 (5)	4 (6)	26 (5)	0.764
Norepinephrine	15 (3)	1 (1.5)	14 (3)	1.000
Vasodilators				
Inhaled nitric oxide	353 (62)	39 (61)	314 (62)	0.892
Sildenafil	126 (22)	12 (19)	114 (22)	0.631
Prostaglandin E1	37 (6)	4 (6)	33 (7)	1.000
Prostacyclin	19 (3)	1 (1.5)	18 (4)	0.711
Bosentan	12 (2)	0 (0)	12 (2)	0.378
ECMO	186 (33)	6 (9)	180 (35)	< 0.001
Total days on ECMO	11 (7, 18)	19 (15, 37)	11 (7, 17)	0.037

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation.
Note: Data presented are *n* (%) or median, (interquartile range).

Additional Short-Term Outcome Metrics

Median hospital LOS was 32 days (IQR 16, 66 days), and correspondingly, 11% of CDH infants had an LOS in excess of 90 days. The use and duration of central venous lines were both frequent (mean of 2 central lines per patient) and prolonged (mean of 20 days per patient), and 9% developed a blood stream infection during their hospitalization. A brain injury was documented on imaging studies in 1.6% of patients, and 19 CDH patients were treated with therapeutic hypothermia for hypoxic–ischemic encephalopathy, of which 10 patients survived. Seizures were common (7.3%) and 3.7% were diagnosed with hearing deficits before discharge. The pharmacologic treatment of gastroesophageal reflux was nearly universal (99.3% of CDH patients), although surgical fundoplication was infrequent (8.1%). Preterm infants were discharged home with supplemental oxygen, diuretic medications, and tube feedings more frequently than infants born near or full term (►**Table 3**).

Discussion

Despite recent advances in medical technology and care, infants with CDH experience significant morbidity and mortality.[1–4] Several groups have examined the management of CDH as well as for identification of factors that predict outcome.[5–11] We describe a large multicenter cohort of CDH infants referred to regional NICUs for care with an emphasis on the medical therapy provided because these therapies in a large contemporary cohort have not been well described. Better understanding of the variability in practice and center-specific practices as they relate to outcome may ultimately help to identify best practices that may improve outcomes for affected infants.

Although prematurity has been identified as an independent predictor of adverse outcomes in CDH,[17,18] relatively few studies have examined this group of CDH patients in detail. Our cohort shows that infants born < 34 weeks' gestation or < 2 kg in weight are as likely to receive aggressive care as more mature infants, with the exception of ECMO. Overall, the preterm, smaller infants received respiratory support and ECMO therapy for a longer duration. We also found that CDH infants born prematurely more commonly had a right-sided CDH, and previous reports have shown that these infants are more likely to have associated anomalies[17]; both risk factors associated with mortality.[7,19,20] Clearly, preterm infants with CDH represent an

Table 3 Predischarge outcomes in infants with CDH

Variable	All ($N = 572$)	< 34 wk or < 2 kg ($n = 64$)	≥ 34 wk and ≥ 2 kg ($n = 508$)	p Value
Mortality, n (%)	167 (29)	32 (50)	135 (27)	< 0.001
Median hospital length of stay (IQR)	32 (16, 66)	40 (5, 76)	32 (17, 63)	0.890
CDH patients discharged home	356 (66)	21 (33)	352 (69)	
Route of feed at discharge				
Breast	139 (40)	6 (29)	133 (41)	0.259
Bottle	255 (74)	15 (71)	240 (74)	0.789
Tube[a]	142 (41)	15 (71)	127 (39)	0.004
Bottle and tube[a]	73 (21)	9 (43)	64 (20)	0.012
Discharge medications				
Supplemental oxygen	83 (24)	10 (48)	73 (23)	0.009
Sildenafil	47 (14)	5 (24)	42 (13)	0.158
Furosemide	24 (7)	5 (24)	19 (6)	0.002
Thiazide	22 (6)	4 (19)	18 (6)	0.036

Abbreviation: CDH, congenital diaphragmatic hernia.
[a]Includes gastrostomy, nasogastric, or transpyloric administration of feedings. Data presented are n (%) or median (interquartile range).

extremely high-risk group of patients, with a higher morbidity and mortality than more mature infants.

In our cohort, the survival of preterm infants was 50%, which included one infant treated with ECMO. For those preterm infants who survived, more were discharged on oxygen or with feeding assistance than mature infants, but with comparable rates of documented brain injury, seizures, and hearing loss. Although increased risk of long-term morbidity must be considered in this population, counseling and overall approach to care of preterm infants with CDH should balance this risk with the likelihood of short-term survival—and the burdens of lengthy hospitalizations—when considering aggressive treatment.

Overall survival in this group of patients referred for care of CDH was 71%, similar to that in previous reports.[1,4,10,12] As expected, the majority of nonsurvivors died as a result of pulmonary hypoplasia, pulmonary hypertension, and cardiopulmonary failure. Nonsurvivors were treated with more medical therapies including HFOV, vasopressors, pulmonary vasodilator medications, and ECMO despite uncertain efficacy to increase the likelihood of survival. Interestingly, we did find that after referral to regional NICUs, only a single nonsurvivor was not mechanically ventilated, suggesting that these infants are nearly universally offered aggressive intervention. Despite this, mortality remains high for this condition. Continued efforts to define those infants least likely to respond to aggressive medical and surgical intervention are warranted.

Despite a high risk of morbidity related to treatment of CDH, we found that in-hospital outcomes for survivors were relatively favorable. Specifically, surgical, infectious, and neurologic complications existed, but they were infrequent, and the majority of patients were discharged home without supplemental oxygen or medications to treat pulmonary hypertension. This cohort of infants was treated with many medical therapies, for which evidence is limited or incomplete, including inhaled nitric oxide, sildenafil, diuretic medications, and acid suppression medications for gastroesophageal reflux during their initial hospital course.[19–26] Use of this data in conjunction with additional prospective studies may help to determine most effective practices for medical management of CDH.

There are limitations of this study that surround the issue of referral bias. This cohort referred to regional NICUs may not be representative of the entire population of infants with CDH; it is plausible that the infants who were most likely to experience complications or poor outcomes associated with CDH were referred to these NICUs. Alternatively, infants deemed as nonsurvivable, whether term or preterm, may have remained at the referral hospital and not transferred for aggressive care. Nevertheless, this report summarizes the therapies received and the short-term outcomes of a large, contemporary, US-born cohort of infants with CDH referred to participating children's hospitals' NICUs to provide data for counseling families of affected infants.

In summary, these results facilitate a greater understanding of the burden CDH infants face, both for clinicians and for families of affected infants. Although individual hypotheses were not tested, these data serve to generate hypotheses on which future prediction and prospective studies will be based. Moreover, these results demonstrate the successful collaboration between 27 hospitals in the United States focused on high-risk infants with complex diseases and rare conditions. Specifically, these data provide the framework for future studies to predict short-term outcomes using clinical risk factors as well as to quantify the intercenter variation in care delivered and outcomes achieved between these regional NICUs.

Table 4 Therapies utilized by CDH patients during initial hospitalization

Variable	All ($N = 572$)	Survivors ($n = 405$)	Nonsurvivors ($n = 167$)	p Value
Advanced respiratory support				
Median days on mechanical ventilation (median, IQR)	15 (6, 29)	15 (7, 29)	15.5 (2, 27)	0.013
High frequency oscillatory ventilation, *N* (%)	347 (61)	199 (49)	148 (89)	< 0.001
Median duration in days	5 (2, 13)	6 (2, 13)	3.5 (1, 14)	0.039
High-frequency jet ventilation	11 (2)	6 (1.5)	5 (3)	0.31
Median duration in days	4 (1, 9)	2 (1, 4)	9 (6, 15)	0.016
Conventional ventilation	510 (89)	385 (95)	125 (75)	< 0.001
Median duration in days	12 (5, 23)	12 (6, 23)	10 (3, 22)	0.009
Vasopressors				
Dopamine	419 (73)	271 (67)	148 (89)	< 0.001
Epinephrine	192 (34)	103 (25)	89 (53)	< 0.001
Milrinone	172 (30)	91 (22)	81 (49)	< 0.001
Dobutamine	76 (13)	36 (9)	40 (24)	< 0.001
Vasopressin	30 (5)	18 (4)	12 (7)	0.215
Norepinephrine	15 (3)	11 (3)	4 (2)	1.000
Vasodilators				
Sildenafil	126 (22)	81 (20)	45 (27)	0.076
Prostaglandin E1	37 (6)	19 (5)	18 (11)	0.014
Inhaled Prostacyclin	19 (3)	9 (2)	10 (6)	0.036
IV Prostacyclin	19 (3)	7 (2)	12 (7)	0.003
Bosentan	12 (2)	7 (2)	5 (3)	0.346
ECMO	186 (33)	95 (23)	91 (54)	< 0.001
Total days on ECMO	11 (7, 18)	9 (6, 14)	14 (9, 21)	< 0.001
VV	42 (7)	22 (5)	20 (12)	0.012
VA	140 (24)	72 (18)	68 (41)	< 0.001
VV-VA	7 (1.2)	2 (0.5)	5 (3.0)	0.025

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VV, venovenous; VV-VA, venovenous converted to venoarterial.
Note: Data presented are *n* (%) or median (interquartile range).

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