Published in final edited form as:

Am J Perinatol. 2015 July ; 32(9): 887–894. doi:10.1055/s-0035-1544949.

Management Practice and Mortality for Infants with Congenital Diaphragmatic Hernia

Jonathan R. Malowitz, MD^{1,2}, Christoph P. Hornik, MD, MPH^{1,2}, Matthew M. Laughon, MD, MPH³, Daniela Testoni, MD, MHS^{2,4}, C. Michael Cotten, MD, MHS¹, Reese H. Clark, MD⁵, and P. Brian Smith, MD, MPH, MHS^{1,2}

¹Department of Pediatrics, Duke University Medical Center, Durham, North Carolina

²Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina

³Department of Pediatrics, North Carolina Children's Hospital, Chapel Hill, North Carolina

⁴Division of Neonatal Medicine, Escola Paulista de Medicina – Universidade Federal de São Paulo, São Paulo, Brazil

⁵Pediatric Medical Group, Sunrise, Florida

Abstract

Objective—Congenital diaphragmatic hernia (CDH) is fatal in 20–40% of cases, largely due to pulmonary dysmaturity, lung hypoplasia, and persistent pulmonary hypertension. Evidence for survival benefit of inhaled nitric oxide (iNO), extracorporeal membrane oxygenation (ECMO), and other medical interventions targeting pulmonary hypertension is lacking. We assessed medical interventions and mortality over time in a large multicenter cohort of infants with CDH.

Study Design—We identified all infants < 34 weeks gestation with CDH discharged from 29 neonatal intensive care units between 1999 and 2012 with an average of 2 CDH admissions per year. We examined mortality and the proportion of infants exposed to medical interventions, comparing 4 periods of time: 1999–2001, 2002–2004, 2005–2007, and 2008–2012.

Results—We identified 760 infants with CDH. From 1999–2001 to 2008–2012, use of iNO increased from 20% of infants to 50%, sildenafil use increased from 0% to 14%, and milrinone use increased from 0% to 22% ($p < 0.001$). Overall mortality (28%) did not significantly change over time compared with the earliest time period.

Conclusions—Despite changing use of iNO, sildenafil, and milrinone, CDH mortality has not significantly decreased in this population of infants.

Keywords

infants; congenital diaphragmatic hernia; lung dysmaturity; lung hypoplasia; pulmonary hypertension; respiratory management

Address for correspondence: P. Brian Smith, MD, MPH, MHS, Associate Professor of Pediatrics, Duke Clinical Research Institute, Box 17969, Durham, NC 27715 (phone: 919-668-8951; brian.smith@duke.edu).

The authors have no potential conflicts of interest to disclose.

Congenital diaphragmatic hernia (CDH) occurs in 1/2000 to 1/5000 live births and is associated with high mortality and long-term morbidities.^{1–3} Mortality varies by center, with reports ranging from 20–40%.^{4–6} Common causes of postnatal mortality include associated congenital anomalies, pulmonary hypoplasia, persistent pulmonary hypertension (PPHN), and lung dysmaturity.^{4, 7, 8} Patients at higher risk of mortality include those with low birth weight, low 5-minute Apgar score, and prematurity.^{9, 10} Patients who survive beyond discharge are at high risk of multiple morbidities including chronic lung disease, gastroesophageal reflux, growth failure, hearing loss, and poor neurodevelopmental outcomes.^{6, 11–19}

Historical treatment of CDH involving aggressive respiratory management, including ventilation strategies that produced normal PaCO₂ or respiratory alkalosis to facilitate pulmonary vasodilation, was associated with survival of ~50%.^{20–22} These results led to the adoption of gentle ventilation approaches tolerating lower postductal PaO₂ and higher PaCO₂ levels during the first postnatal transition days, incorporating pressure limits for conventional ventilation, and rescue approaches including high-frequency ventilation (HFV) and extracorporeal membranous oxygenation (ECMO).²³ Single centers report that these lung protective strategies resulted in improved survival compared to historical controls.^{4, 6, 24–26} Other therapies that target lung dysmaturity and pulmonary hypertension, including inhaled nitric oxide (iNO), sildenafil, and surfactant, are understudied and, as some studies suggest, possibly deleterious.^{4, 27–30}

The purpose of this study is to examine the use of medical interventions directed at lung dysmaturity, lung hypoplasia, and pulmonary hypertension in a large, multicenter cohort that represents gentle ventilation strategies. Additionally, we sought to describe mortality and medical interventions at discharge over time.

Methods

Study Cohort

We identified all infants < 34 weeks gestation with CDH admitted in the first 2 postnatal days and discharged from 29 neonatal intensive care units (NICUs) managed by the Pediatrix Medical Group between 1999 and 2012. These NICUs encompass both academic and community settings as well as different acuity levels. Only NICUs with an average of 2 CDH admissions per year were included. We excluded infants transferred to other facilities in the first week of life as they likely represented transfers to higher-level-of-care NICUs and had unknown clinical outcomes. Data were obtained from an administrative database that prospectively captures information from a shared electronic medical record including orders, laboratory results, and notes generated daily by clinicians.³¹ Data collected included demographic information, medication exposure, respiratory support, ECMO use, and outcomes including mortality. Permission to conduct this analysis was provided by the Duke University Institutional Review Board.

Definitions

CDH was diagnosed by the provider. We defined medical interventions as any exposure to surfactant, iNO, sildenafil, bosentan, milrinone, prostaglandin E1 (PGE1), HFV, or ECMO at any time during hospitalization. We defined mortality as death prior to hospital discharge. We defined discharge interventions as gastrostomy tube placement and exposure to supplemental oxygen, diuretics (furosemide, bumetanide, spironolactone, chlorothiazide, ethacrynic acid), bronchodilators (albuterol, levalbuterol, budesonide), sildenafil, bosentan, histamine 2 receptor antagonists (H2 antagonists; ranitidine, cimetidine, famotidine), proton pump inhibitors (PPIs; omeprazole, lansoprazole, pantoprazole), or prokinetics (metoclopramide, erythromycin, baclofen) at the time of discharge to home. Patients not discharged to home were excluded from analysis of discharge interventions. We report change in medical interventions, discharge interventions, and mortality over 4 time periods: 1999–2001, 2002–2004, 2005–2007, and 2008–2012.

Statistical Methods

We report continuous variables as medians and interquartile ranges and categorical variables as counts and proportions. We compared the proportion of infants over time using chi-square tests of association and Cochran Armitage tests for trend. We calculated the unadjusted odds of mortality by time period using the earliest time period as a reference. We calculated the adjusted odds of mortality by controlling for birth weight, 5-minute Apgar score, and prematurity (< 37 weeks gestation). We conducted all analyses using Stata 12 (College Station, TX) and considered a $p < 0.05$ statistically significant.

Results

Demographics

We identified 760 infants with CDH from 29 NICUs; these infants had a median gestational age of 38 weeks (interquartile range: 37, 39) and median birth weight of 2992 g (2635, 3370). We excluded 684 infants transferred in the first week of life. There was an increase in Cesarean sections in the most recent time period, otherwise there were no significant changes in patient demographics during the study period (Table 1). Other major congenital anomalies were present in 258/760 (34%) of the cohort. This proportion increased over the study period (25/92 [27%] in 1999–2001, 44/147 [30%] in 2002–2004, 62/200 [31%] in 2005–2007, and 127/321 [40%] in 2008–2012, $p = 0.04$). The median number of CDH admissions per site was 16 (11, 35) with a maximum of 130.

Management

Medical interventions that increased in frequency during the study period included sildenafil, milrinone, and iNO (Fig. 1). Medical interventions that did not change from 1999–2001 to 2008–2012 included use of surfactant (16/92 [17%] vs. 47/321 [15%], $p = 0.23$); bosentan (0/92 [0%] vs. 3/321 [1%], $p = 0.51$); HFV (58/92 [63%] vs. 202/321 [63%], $p = 0.44$); ECMO (20/92 [22%] vs. 65/321 [20%], $p = 0.70$); and PGE1 (5/192 [5%] vs. 21/321 [7%], $p = 0.32$).

Discharge Interventions and Mortality

Overall mortality during the study period was 202/760 (27%). Mortality did not significantly change between 1999–2001 and 2008–2012 (Fig. 2). Using the first time period as a reference, unadjusted odds of mortality were not significantly changed over time: 2002–2004 OR=0.91 (95% confidence interval, 0.50–1.66); 2005–2007, OR=1.12 (0.64–1.95); and 2008–2012, OR=0.83 (0.49–1.42). Unadjusted odds of mortality comparing the last 3 time periods combined (2002–2012) to the first time period (1999–2001) was 0.93 (0.57–1.53). Similarly, mortality for patients treated with ECMO did not vary significantly between 1999–2001 and 2008–2012: 8/19 (42%) vs. 28/59 (48%), $p=0.50$.

Odds of mortality were adjusted for birth weight, 5-minute Apgar score, and prematurity. Using the first time period as a point of reference, there was no change in adjusted odds of mortality over time: 2002–2004, OR=0.69 (95% confidence interval, 0.35–1.33); 2005–2007, OR=0.89 (0.48–1.67); and 2008–2012, OR=0.65 (0.35–1.18). Adjusted odds of mortality comparing the last 3 time periods combined (2002–2012) to the first time period (1999–2001) were 0.72 (0.41–1.27).

Infants who survived to discharge ($n=516$) had a median length of stay of 32 days (21, 55). Infants who died ($n=202$) had a median length of stay of 4 days (2, 21), with 80/202 (40%) dying in the first 24 hours of life and only 4 of those (5%) receiving ECMO. Infants who received ECMO and died were older at the time of death compared to those infants who did not receive ECMO and died (median postnatal age at death 20 days [12, 29] vs. 1 day [0, 3], $p<0.001$). Length of stay for non-ECMO survivors was 28 days (19, 43) and, for infants who survived to discharge after ECMO, was 73 days (54, 97). Of the infants discharged home, 219/474 (46%) required at least 1 discharge intervention (Table 2). There was an increase in the number of infants discharged home with at least 1 discharge intervention: 16/58 (28%) vs. 102/219 (47%), $p=0.01$. There was no significant change in any of the respiratory discharge interventions over time. There was a significant increase over time in the proportion of infants discharged with gastrostomy tubes, prokinetic agents, and antacid therapy.

Discussion

We found that CDH mortality did not change significantly from 1999–2012 in a large cohort of infants admitted to a NICU. This population represents the era after implementation of gentle ventilation strategies.^{32, 33} The use of iNO, sildenafil, and milrinone increased, while the use of surfactant, HFV, bosentan, and ECMO remained stable over the study time period. In addition, we found that an increasing number of infants with CDH are discharged with gastrostomy tubes, prokinetic agents, and antacid therapy.

Although iNO is labeled by the Food and Drug Administration (FDA) as effective in treating pulmonary hypertension in infants with respiratory failure, the efficacy in infants with CDH is unknown.^{27, 34} iNO activates guanylate cyclase leading to smooth muscle relaxation and a strong vasodilatory effect in the pulmonary vasculature. Results from randomized trials of iNO for hypoxic respiratory failure in term infants, including infants with CDH, demonstrated an increased frequency of ECMO use for the subgroup of infants

with CDH exposed to iNO vs. placebo.^{27, 28, 34} However, single centers have reported improved survival with the introduction of iNO, though protective lung ventilation strategies were introduced concurrently potentially confounding the iNO effect.^{35, 36} Our data demonstrate that despite the evidence for harm and lack of evidence for efficacy, iNO use has significantly increased.

Sildenafil is a phosphodiesterase inhibitor that relaxes pulmonary vasculature.^{37, 38} The FDA recently published a boxed warning on sildenafil use in pediatric patients based on a study of children 1 to 17 years of age with pulmonary hypertension and congenital heart disease that suggested an increased mortality risk at higher doses with little benefit at lower doses.³⁹ However, the risk only became apparent after two years of treatment in the high dose group of subjects.⁴⁰ While studies of sildenafil in CDH patients is limited,^{30, 41} use of sildenafil also increased over the time period of our study.

In a case series of 6 patients with CDH and PPHN, milrinone—another phosphodiesterase inhibitor—improved systolic and diastolic function.⁴² However, no prospective studies exist for infants with PPHN or CDH.⁴³ Furthermore, milrinone's effect of lowering systemic vascular resistance⁴⁴ may counteract efforts to raise systemic blood pressure in infants with CDH and PPHN. Bosentan, a dual endothelin receptor antagonist, has been used in one reported case of refractory PPHN in an infant with CDH.⁴⁵ This limited experience in CDH patients is reflected in our data where only 5 infants were treated with bosentan.

Maintaining patency of the ductus arteriosus with PGE1 allows the pressure- and/or volume-overloaded right ventricle to unload to the system circulation.⁴⁶ However, the few reported studies of patients with CDH treated with PGE1 suggest an improvement in left ventricular function but longer delay to surgery and longer hospital stay.^{46–48} In our cohort, PGE1 was used in 5% of infants with CDH and did not significantly change over time. Surfactant has not been shown to improve survival in CDH⁴⁹ and may worsen outcomes, including death and need for ECMO.^{4, 29} In our study, surfactant use did not change over the study period with 15–17% of infants receiving the medication.

Reported frequency of ECMO use in infants with CDH ranges between 11% and 61%,⁴ while ECMO use in our population was 22%. Reported mortality among CDH infants treated with ECMO ranges between 40% and 60%, with better results reported at higher volume centers.^{4–7, 50, 51} Additionally, ECMO is associated with neuromotor disabilities both owing to the severity of the underlying disease and the increase risk for intracranial hemorrhage and stroke.^{52–54}

Reports of CDH mortality vary widely owing to variation in practices and the type of reports. Single centers report mortality as low as 10%.⁴ Many of these centers are high volume, which tends to improve outcomes.⁵⁵ Overall mortality in our multicenter-based population was 28%.

While mortality did not vary, discharge interventions were evaluated to assess if morbidity of surviving infants improved. Among survivors in our dataset, home oxygen use did not change over time while there was an increase in gastroesophageal reflux treatments and gastrostomy tube placement. The incidence of chronic lung disease in CDH patients vary

from 13% to 50%^{6, 24} with up to 21% requiring oxygen after discharge.¹⁶ In our population, there were no significant changes in respiratory interventions used at discharge. Gastroesophageal reflux incidence has been reported to be >60% in infants with CDH with many infants requiring medication, gastrostomy tube placement, or fundoplication.^{17, 19} Patients with larger defects requiring patch repair or those who require ECMO are at higher risk for gastrostomy placement.⁵⁶ In our database we found significant increases in gastrointestinal interventions at discharge, although ECMO use in our cohort did not change over time.

We were not able to track patients between non-Pediatrix sites and sites included in the Pediatrix group. This led to the exclusion of a high proportion of infants transferred in the first week of life, potentially limiting our ability to identify changes in outcomes associated with newer or more aggressive interventions that these infants may have received. However, the proportion of infants transferred in the first week of life remained stable over time: 40% in 1999–2001, 40% in 2002–2004, 37% in 2005–2007, and 39% in 2008–2012, $p=0.90$). This finding suggests that the lack of change in outcomes over time is not due to a changing proportion of infants being transferred in the first week of life. We also did not have access to anatomic details, such as side of lesion, presence of liver herniation, or type of surgical repair. Although the data do not allow for determination of the ventilation strategies used at each site, the study period occurred at a time when there was widespread adoption of gentle ventilation strategies. Site information does not include the level of care (e.g., level III vs. IV). However, the admission inclusion criterion and the transfer exclusion criterion limit this cohort to centers that care for critically ill infants with CDH.

Despite the introduction of new medications, mortality has remained relatively unchanged since the advent of lung-protective strategies. Quantifying the safety and efficacy of interventions such as sildenafil, milrinone, PGE1, bosentan, and iNO in infants with CDH requires randomized clinical trials or prospective cohort studies of comparative effectiveness with careful data collection characterizing the infants and their outcomes.

Acknowledgments

Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) under award number UL1TR001117. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Dr. Smith receives salary support for research from the NIH and the National Center for Advancing Translational Sciences of the NIH (HHSN267200700051C, HHSN275201000003I, and UL1TR001117); he also receives research support from industry for neonatal and pediatric drug development (www.dcri.duke.edu/research/coi.jsp). Dr. Laughon receives support from the U.S. government for his work in pediatric and neonatal clinical pharmacology (Government Contract HHSN267200700051C, PI: Benjamin under the Best Pharmaceuticals for Children Act) and from the National Institute of Child Health and Human Development (K23HD068497). Dr. Hornik receives salary support for research from the National Center for Advancing Translational Sciences of the National Institutes of Health (UL1TR001117).

Abbreviations

CDH	congenital diaphragmatic hernia
ECMO	extracorporeal membrane oxygenation

HFV	high-frequency ventilation
iNO	inhaled nitric oxide
NICUs	neonatal intensive care units
PPHN	persistent pulmonary hypertension

References

1. Colvin J, Bower C, Dickinson JE, Sokol J. Outcomes of congenital diaphragmatic hernia: a population-based study in Western Australia. *Pediatrics*. 2005; 116(3):e356–e363. [PubMed: 16140678]
2. Langham MR Jr, Kays DW, Ledbetter DJ, et al. Congenital diaphragmatic hernia. Epidemiology and outcome. *Clin Perinatol*. 1996; 23(4):671–688. [PubMed: 8982563]
3. Philip N, Gambarelli D, Guys JM, Camboulives J, Ayme S. Epidemiological study of congenital diaphragmatic defects with special reference to aetiology. *Eur J Pediatr*. 1991; 150:726–729. [PubMed: 1915486]
4. Logan JW, Rice HE, Goldberg RN, Cotten CM. Congenital diaphragmatic hernia: a systematic review and summary of best-evidence practice strategies. *J Perinatol*. 2007; 27:535–549. [PubMed: 17637787]
5. Seetharamaiah R, Younger JG, Bartlett RH, Hirschl RB. Factors associated with survival in infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: a report from the Congenital Diaphragmatic Hernia Study Group. *J Pediatr Surg*. 2009; 44:1315–1321. [PubMed: 19573654]
6. van den Hout L, Schaible T, Cohen-Overbeek TE, et al. Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol. *Fetal Diagn Ther*. 2011; 29(1):55–63. [PubMed: 21325859]
7. Abdullah F, Zhang Y, Sciortino C, et al. Congenital diaphragmatic hernia: outcome review of 2,173 surgical repairs in US infants. *Pediatr Surg Int*. 2009; 25:1059–1064. [PubMed: 19727769]
8. George DK, Cooney TP, Chiu BK, Thurlbeck WM. Hypoplasia and immaturity of the terminal lung unit (acinus) in congenital diaphragmatic hernia. *Am Rev Respir Dis*. 1987; 136:947–950. [PubMed: 3662245]
9. Congenital Diaphragmatic Hernia Study Group. Estimating disease severity of congenital diaphragmatic hernia in the first 5 minutes of life. *J Pediatr Surg*. 2001; 36:141–145. [PubMed: 11150453]
10. Tsao K, Allison ND, Harting MT, Lally PA, Lally KP. Congenital diaphragmatic hernia in the preterm infant. *Surgery*. 2010; 148:404–410. [PubMed: 20471048]
11. Rocha G, Azevedo I, Pinto JC, Guimaraes H. Follow-up of the survivors of congenital diaphragmatic hernia. *Early Hum Dev*. 2012; 88:255–258. [PubMed: 21945360]
12. Lally KP, Engle W. American Academy of Pediatrics Section on S, American Academy of Pediatrics Committee on F, Newborn. Postdischarge follow-up of infants with congenital diaphragmatic hernia. *Pediatrics*. 2008; 121:627–632. [PubMed: 18310215]
13. Friedman S, Chen C, Chapman JS, et al. Neurodevelopmental outcomes of congenital diaphragmatic hernia survivors followed in a multidisciplinary clinic at ages 1 and 3. *J Pediatr Surg*. 2008; 43:1035–1043. [PubMed: 18558179]
14. Muratore CS, Kharasch V, Lund DP, et al. Pulmonary morbidity in 100 survivors of congenital diaphragmatic hernia monitored in a multidisciplinary clinic. *J Pediatr Surg*. 2001; 36:133–140. [PubMed: 11150452]
15. Ng GY, Derry C, Marston L, Choudhury M, Holmes K, Calvert SA. Reduction in ventilator-induced lung injury improves outcome in congenital diaphragmatic hernia? *Pediatr Surg Int*. 2008; 24:145–150. [PubMed: 17973115]

16. van den Hout L, Reiss I, Felix JF, et al. Risk factors for chronic lung disease and mortality in newborns with congenital diaphragmatic hernia. *Neonatology*. 2010; 98:370–380. [PubMed: 21042035]
17. Maier S, Zahn K, Wessel LM, Schaible T, Brade J, Reinshagen K. Preventive antireflux surgery in neonates with congenital diaphragmatic hernia: a single-blinded prospective study. *J Pediatr Surg*. 2011; 46:1510–1515. [PubMed: 21843716]
18. Morini F, Capolupo I, Masi R, et al. Hearing impairment in congenital diaphragmatic hernia: the inaudible and noiseless foot of time. *J Pediatr Surg*. 2008; 43:380–384. [PubMed: 18280294]
19. Muratore CS, Utter S, Jaksic T, Lund DP, Wilson JM. Nutritional morbidity in survivors of congenital diaphragmatic hernia. *J Pediatr Surg*. 2001; 36:1171–1176. [PubMed: 11479850]
20. Azarow K, Messineo A, Pearl R, Filler R, Barker G, Bohn D. Congenital diaphragmatic hernia—a tale of two cities: the Toronto experience. *J Pediatr Surg*. 1997; 32:395–400. [PubMed: 9094001]
21. Bagolan P, Casaccia G, Crescenzi F, Nahom A, Trucchi A, Giorlandino C. Impact of a current treatment protocol on outcome of high-risk congenital diaphragmatic hernia. *J Pediatr Surg*. 2004; 39:313–318. [PubMed: 15017544]
22. Bohn D. Congenital diaphragmatic hernia. *Am J Respir Crit Care Med*. 2002; 166:911–915. [PubMed: 12359645]
23. Wung JT, James LS, Kilchevsky E, James E. Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. *Pediatrics*. 1985; 76:488–494. [PubMed: 4047792]
24. Rocha GM, Bianchi RF, Severo M, et al. Congenital diaphragmatic hernia - the neonatal period (part I). *Eur J Pediatr Surg*. 2008; 18:219–223. [PubMed: 18704887]
25. Rozmiarek AJ, Qureshi FG, Cassidy L, Ford HR, Hackam DJ. Factors influencing survival in newborns with congenital diaphragmatic hernia: the relative role of timing of surgery. *J Pediatr Surg*. 2004; 39:821–824. [PubMed: 15185204]
26. Tracy ET, Mears SE, Smith PB, et al. Protocolized approach to the management of congenital diaphragmatic hernia: benefits of reducing variability in care. *J Pediatr Surg*. 2010; 45:1343–1348. [PubMed: 20620342]
27. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. *Cochrane Database Syst Rev*. 2006:CD000399. [PubMed: 17054129]
28. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. The Neonatal Inhaled Nitric Oxide Study Group (NINOS). *Pediatrics*. 1997; 99:838–845. [PubMed: 9190553]
29. Van Meurs K. Is surfactant therapy beneficial in the treatment of the term newborn infant with congenital diaphragmatic hernia? *J Pediatr*. 2004; 145:312–316. [PubMed: 15343181]
30. Noori S, Friedlich P, Wong P, Garingo A, Seri I. Cardiovascular effects of sildenafil in neonates and infants with congenital diaphragmatic hernia and pulmonary hypertension. *Neonatology*. 2007; 91:92–100. [PubMed: 17344658]
31. Downey LC, Benjamin DK Jr, Clark RH, et al. Urinary tract infection concordance with positive blood and cerebrospinal fluid cultures in the neonatal intensive care unit. *J Perinatol*. 2013; 33:302–306. [PubMed: 22935772]
32. Frenckner 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. [PubMed: 9269967]
33. Wung JT, Sahni R, Moffitt ST, Lipsitz E, Stolar CJ. Congenital diaphragmatic hernia: survival treated with very delayed surgery, spontaneous respiration, and no chest tube. *J Pediatr Surg*. 1995; 30:406–409. [PubMed: 7760230]
34. Jacobs P, Finer NN, Robertson CM, Etches P, Hall EM, Saunders LD. A cost-effectiveness analysis of the application of nitric oxide versus oxygen gas for near-term newborns with respiratory failure: results from a Canadian randomized clinical trial. *Crit Care Med*. 2000; 28:872–878. [PubMed: 10752844]
35. Downard CD, Jaksic T, Garza JJ, et al. Analysis of an improved survival rate for congenital diaphragmatic hernia. *J Pediatr Surg*. 2003; 38:729–732. [PubMed: 12720181]

36. Kim do H, Park JD, Kim HS, et al. Survival rate changes in neonates with congenital diaphragmatic hernia and its contributing factors. *J Korean Med Sci.* 2007; 22:687–692. [PubMed: 17728511]
37. Baquero H, Soliz A, Neira F, Venegas ME, Sola A. Oral sildenafil in infants with persistent pulmonary hypertension of the newborn: a pilot randomized blinded study. *Pediatrics.* 2006; 117:1077–1083. [PubMed: 16585301]
38. Carroll WD, Dhillon R. Sildenafil as a treatment for pulmonary hypertension. *Arch Dis Child.* 2003; 88:827–828. [PubMed: 12937112]
39. FDA Drug Safety Communication. FDA recommends against use of Revatio in children with pulmonary hypertension. 2012. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm317123.htm>.
40. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naïve children with pulmonary arterial hypertension. *Circulation.* 2012; 125:324–334. [PubMed: 22128226]
41. Hunter L, Richens T, Davis C, Walker G, Simpson JH. Sildenafil use in congenital diaphragmatic hernia. *Arch Dis Child Fetal Neonatal Ed.* 2009; 94:F467. [PubMed: 19846401]
42. Patel N. Use of milrinone to treat cardiac dysfunction in infants with pulmonary hypertension secondary to congenital diaphragmatic hernia: a review of six patients. *Neonatology.* 2012; 102:130–136. [PubMed: 22710735]
43. Bassler D, Kreutzer K, McNamara P, Kirpalani H. Milrinone for persistent pulmonary hypertension of the newborn. *Cochrane Database Syst Rev.* 2010;CD007802. [PubMed: 21069698]
44. Khazin V, Kaufman Y, Zabeeda D, et al. Milrinone and nitric oxide: combined effect on pulmonary artery pressures after cardiopulmonary bypass in children. *J Cardiothorac Vasc Anesth.* 2004; 18:156–159. [PubMed: 15073704]
45. Frenckner B, Broome M, Lindstrom M, Radell P. Platelet-derived growth factor inhibition--a new treatment of pulmonary hypertension in congenital diaphragmatic hernia? *J Pediatr Surg.* 2008; 43:1928–1931. [PubMed: 18926235]
46. Inamura N, Kubota A, Nakajima T, et al. A proposal of new therapeutic strategy for antenatally diagnosed congenital diaphragmatic hernia. *J Pediatr Surg.* 2005; 40:1315–1319. [PubMed: 16080939]
47. Hofmann SR, Stadler K, Heilmann A, et al. Stabilisation of cardiopulmonary function in newborns with congenital diaphragmatic hernia using lung function parameters and hemodynamic management. *Klin Padiatr.* 2012; 224:e1–e10. [PubMed: 22782443]
48. Shiyanagi S, Okazaki T, Shoji H, et al. Management of pulmonary hypertension in congenital diaphragmatic hernia: nitric oxide with prostaglandin-E1 versus nitric oxide alone. *Pediatr Surg Int.* 2008; 24:1101–1104. [PubMed: 18726605]
49. Lally KP, Lally PA, Langham MR, et al. Surfactant does not improve survival rate in preterm infants with congenital diaphragmatic hernia. *J Pediatr Surg.* 2004; 39:829–833. [PubMed: 15185206]
50. Bucher BT, Guth RM, Saito JM, Najaf T, Warner BW. Impact of hospital volume on in-hospital mortality of infants undergoing repair of congenital diaphragmatic hernia. *Ann Surg.* 2010; 252:635–642. [PubMed: 20881770]
51. 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. [PubMed: 9694085]
52. Evans MJ, McKeever PA, Pearson GA, Field D, Firmin RK. Pathological complications of non-survivors of newborn extracorporeal membrane oxygenation. *Arch Dis Child.* 1994; 71:F88–F92. [PubMed: 7979484]
53. Hanekamp MN, Mazer P, van der Cammen-van Zijp MH, et al. Follow-up of newborns treated with extracorporeal membrane oxygenation: a nationwide evaluation at 5 years of age. *Crit Care.* 2006; 10:R127. [PubMed: 16961935]

54. McNally H, Bennett CC, Elbourne D, Field DJ. UK Collaborative ECMO Trial Group. United Kingdom collaborative randomized trial of neonatal extracorporeal membrane oxygenation: follow-up to age 7 years. *Pediatrics*. 2006; 117(5):e845–e854. [PubMed: 16636114]
55. Grushka JR, Laberge JM, Puligandla P, Skarsgard ED. Canadian Pediatric Surgery Network. Effect of hospital case volume on outcome in congenital diaphragmatic hernia: the experience of the Canadian Pediatric Surgery Network. *J Pediatr Surg*. 2009; 44:873–876. [PubMed: 19433160]
56. Su W, Berry M, Puligandla PS, Aspirot A, Flageole H, Laberge JM. Predictors of gastroesophageal reflux in neonates with congenital diaphragmatic hernia. *J Pediatr Surg*. 2007; 42:1639–1643. [PubMed: 17923189]

Figure 1.

Medical interventions that increased in frequency over the study period. *p < 0.05 relative to 1999–2001.

Figure 2.
Mortality during the study period.

Table 1

Demographics by discharge year, N (%)

	1999-2001 N=92	2002-2004 N=147	2005-2007 N=200	2008-2012 N=321	Total N=760	P
Gestational age, weeks						0.26
<37	14 (15)	33 (22)	36 (18)	49 (15)	132 (17)	
Birth weight, g						0.78
<1500	0 (0)	1 (<1)	2 (1)	3 (1)	6 (1)	
1500-2499	12 (13)	27 (18)	32 (16)	57 (18)	128 (17)	
2500-3499	59 (64)	95 (65)	132 (66)	195 (61)	481 (63)	
3500	21 (23)	24 (16)	33 (17)	66 (21)	144 (19)	
Male	53 (58)	80 (55)	100 (50)	178 (56)	411 (54)	0.52
Race/ethnicity						0.06
White	54 (64)	78 (56)	94 (50)	149 (49)	375 (52)	
Black	4 (5)	12 (9)	25 (8)	18 (6)	49 (7)	
Hispanic	35 (29)	49 (35)	68 (36)	117 (38)	259 (36)	
Other	2 (2)	1 (1)	10 (5)	22 (7)	35 (5)	
Caesarian section	35 (38)	58 (39)	74 (37)	159 (50)	326 (43)	0.009
Inborn	51 (55)	80 (57)	125 (63)	194 (60)	450 (60)	0.59
5-minute Apgar						0.09
0-3	2 (2)	9 (6)	15 (8)	26 (8)	52 (7)	
4-6	19 (21)	34 (23)	54 (28)	56 (18)	163 (22)	
7-10	71 (77)	102 (70)	127 (65)	225 (73)	525 (71)	

Table 2

Discharge interventions, N (%)

	1999–2001 N=58	2002–2004 N=81	2005–2007 N=116	2008–2012 N=219	Total N=474	P
Respiratory						
Oxygen	11 (19)	14 (17)	18 (16)	34 (16)	77 (16)	0.92
Diuretics	3 (5)	4 (5)	5 (4)	16 (7)	28 (6)	0.68
Bronchodilators	1 (2)	1 (1)	3 (3)	9 (4)	14 (3)	0.53
Sildenafil	0	0	4 (3)	11 (5)	15 (3)	0.07
Gastrointestinal						
Gastrostomy tube	2 (3)	7 (9)	13 (11)	47 (18)	69 (12)	0.001
Antacids	1 (2)	6 (7)	22 (19)	46 (21)	75 (16)	<0.001
H2 antagonists	1 (2)	6 (7)	12 (10)	19 (9)	38 (8)	0.25
PPI	0	0	10 (9)	28 (13)	41 (7)	<0.001
Prokinetics	3 (5)	2 (2)	22 (19)	17 (8)	44 (9)	<0.001

Abbreviations: H2 antagonists, histamine H2 receptor antagonists; PPI, proton pump inhibitor.