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**Neurodevelopmental outcome in congenital diaphragmatic hernia: Evaluation, predictors and outcome**

Danzer E *et al.* Neurological outcome in CDH

Enrico Danzer, Stephen S Kim

**Enrico Danzer, Stephen S Kim,** Division of Pediatric Surgery, Department of Surgery, Inova Fairfax Hospital for Children and the Virginia Commonwealth University School of Medicine, Fairfax, VA 22003, United States

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**Correspondence to: Stephen S Kim, MD, FACS, FAAP, Clinical Associate Professor** of Surgery, Inova Fairfax Hospital for Children and Virginia Commonwealth University School of Medicine, Pediatric Surgical Group, a Division of FNA, PC, 3301 Woodburn Road, #205 Annandale, VA 22003, United States. skim@pskids.com

**Telephone:** +1-703-5602236 **Fax:** +1-703-8764960

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**Abstract**

To review the reported neurodevelopmental outcome of congenital diaphragmatic hernia (CDH) survivors, identify important predictors of developmental disabilities, and describe the pathophysiological mechanisms contributing to adverse outcome. A Medline search was performed for English-language articles cross-referencing CDH with pertinent search terms. Retrospective, prospective, and longitudinal follow-up studies were examined. The reference lists of identified articles were also searched. Neurodevelopmental dysfunction has been recognized as one of most common and potentially most disabling outcome of CDH. Intelligence appears to be in the low normal to mildly delayed range. Neuromotor dysfunction is common during early childhood. Behavioral problems, hearing impairment, and quality of life related issues are frequently encountered in older children and adolescence. Disease severity correlates with the degree of neurological dysfunction. Neurodevelopmental follow-up in CDH children should become standard of care to identify those who would benefit from early intervention services and improve neurological outcomes.

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**Key words:** Congenital diaphragmatic hernia; Extracorporeal membrane oxygenation; Neurodevelopment; Bayley scale of infant development; Wechsler Preschool and Primary Scale of Intelligenc; Developmental disabilities; Quality of life; Autism

**Core tip:** Neurodevelopmental dysfunction has been recognized as one of the most common comorbitity in congenital diaphragmatic hernia (CDH) and survivors. Disease severity impacts on neurological dysfunction. Neurodevelopmental follow-up in CDH children should become standard of care to improve neurological outcomes.

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**INTRODUCTION**

Congenital diaphragmatic hernia (CDH) is a common anatomical anomaly in which there is herniation of the abdominal viscera into the thoracic cavity due to an incomplete closure of the pleuroperitoneal membrane. It is estimated to occur in approximately 1 in 2500 live births.

Over the past several decades, the postnatal survival rate at tertiary centers has improved with reported rates of 70% to 90%[1,2].Improved survival rates appear to be the result of advances in surgical technique, neonatal intensive care, extracorporeal membrane oxygenation (ECMO), and the widespread implementation of lung preservation ventilation strategies. While improving shot-term morbidity and mortality are important goals, more recent research has focused on long-term outcome as equally important primary outcomes[3-9].

Neurodevelopmental and neurofunctional impairments constitutes one of the most common and most significant morbidity in CDH[10]. There is an increasing concern for considerable delays in various neurological domains: cognitive, motor, language, and visuospatial skills, hearing impairment, and behavioral development[5,10-16].

The purpose of this review is to comprehensively examine the available literature that report on cognitive, motor, and behavioral development in these patients; to identify important predictors of developmental disabilities; and to summarize the pathophysiological mechanisms contributing to adverse outcome.

**COMPREHENSIVE OUTCOME STUDIES**

***Short-term outcome (≤ 36 mo)***

Several studies have evaluated the short-term outcome in CDH children and demonstrated that the neurodevelopmental deficits seen in CDH patients during infancy appears to be comparable to the data reported in infants born with other severe congenital malformation (*e.g.*, congenital heart disease, giant omphalocele, bronchopulmonary dysplasia, preterm infants, and children with deletion 22q11 syndrome)[17-21]. A study by Van Meurs *et al*[22], showed that 25% of CDH children that required ECMO had mild deficits, while seventeen percent showed significant delays. Comparable data were reported by D’Agostino *et al*[23] showing average, mild delays and severe delays in 54%, 23% and 23%, respectively. Bernbaum and associates[14] reported an increased incidence of periventricular leukomalacia and intraventricular hemorrhage (26%), and seizure activity (5%) in CDH survivors. More recently, Cortes *et al*[24] assessed neurocognitive outcomes at 24 mo of age and showed that more than 50% of CDH survivors demonstrated cognitive delays, while nearly 40% were found to have neuromotor dysfunction. Chen *et al*[25] evaluated motor skills in 13 CDH children during early childhood; nearly 80% of participants showed impairments.

In a pilot study of 41 CDH patients enrolled in the Pulmonary Hypoplasia Program at the Children’s Hospital of Philadelphia, Danzer *et al*[12] found at a median of 2 years cognitive and language skills within the average, mild delays, and severe delays in 49%, 36%, and 15% respectively. Motor skills were average in 46% while 23% had mild deficits, and 31% had severe neuromotor deficits. Comparable data were recently reported by Wynn *et al*[26] in a multicenter prospective follow-up study of 48 CDH survivors at 24 mo of age.

***Intermediate-term outcome (37 mo to ≤ 5 years)***

Neurological assessments during school age generally are relatively stable and more predictive of long-term outcome. However, data on preschool neurodevelopmental outcomes is sparse. Nijhuis-van der Sanden *et al*[27] studied neuromotor skills in 32 CDH survivors. Thirty-eight percent had normal scores. A total of 34% had mild delays and sixteen percent had significant problems[27]. In a similar study, van der Cammen-van Zijp *et al*[28] found various degrees of neuromotor delays in 42%.

In one of the largest prospective follow-up study, Danzer and associates[11] followed 60 CDH patients. The majority of CDH children have more favorable neurodevelopmental outcome at early preschool age and performed well within the average range. Twenty-two percent of evaluated CDH patients had borderline scores. Eleven percent showed significant delays in at least one domain[11].

***Long-term outcome (above 5 years of age)***

As children get older, it is possible to assess and study a broader range of neurological function, however analogous to the data shown above, only a few reports focus on school age and adolescence outcome in CDH patients. Bouman and associates[29] studied 11 CDH patients at 10 years of age. Below average IQ scores were found in nearly half of the population. Jacobson and coworkers[16] compared 15 CDH survivors to age-matched controls at a follow-up of 13 years. Although the mean neurodevelopmental and functional scores were similar between groups, nearly one-fourth of the CDH children scored below average. Significant delays were found in 13%.

Similarly, Rasheed *et al*[16] reported the data of CDH survivors that required ECMO either after or before surgical closure of the diaphragm defect. IQ scores for children that had surgery before ECMO were within the average range, while children that underwent ECMO first had below average scores. Overall neurofucntion scores were similar between groups.

Recently, Tureczek *et al*[30] evaluated 33 CDH children without ECMO support at 9 years of age using the WPSSI-III and the Movement Assessment Battery for Children 2nd edition. Although they report that the overall neurocognitive scores were not significantly different than population norms, they reported increased rates of motor dysfunction[30].

The long-term implications of these findings throughout adulthood are uncertain. Continued outcome research is warranted as these children progress through school, since lower academic scores, learning disabilities, and/or the presence of behavioral problems, might be associated with increased risk of school failure which in turn may lead to poor social skills, low self-esteem, disinhibition, and delinquency. Of note, the improvements in perinatal care of CDH neonates in the past decade coupled with the improved understanding of the pathophysiological sequelae associated with CDH may make it difficult to extrapolate the reported data in currently school-age children to newborns born in the past decade. It is likely that current CDH survivors will have better neurological outcomes than those born just a generation or two before.

***Longitudinal outcome***

Similar to the lack of long-term outcome data, there is a paucity of longitudinal assessments. Longitudinal evaluations are important as it has been acknowledged that several neurodevelopmental disabilities may be transient, while others may continue to evolve later in life when more complex cognitive and executive performances are required.

To date, only three studies reporting on the longitudinal neurodevelopmental outcome in CDH. Gischler *at al*[31] evaluated 12 CDH infants every six months for the first two years of life. Cognitive and language scores at 6 and 24 mo were average. Neuromotor scores slightly improved from the low-average range to the average range.

Friedman *et al*[32] followed 23 CDH survivors during the first three years of life. Of the 17 children noted to have neurofunctional problems at three years of age, 13 had already variable degrees of neurofunctional impairments at one year.

In 2013, Danzer *et al*[10] longitudinally evaluated the neurodevelopmental outcome of 47 CDH children in the first three years of age. During the study period, BSID-III neurodevelopmental and motor scores improved in 19% and 37%, respectively. In spite of the performance improvements, the number of CDH patients with mild to severe delays in at least one neurodevelopmental area was greater than expected for the general population[10]. Seventy-two percent of the children scored within the average range for all three domains, while 17% were delayed in either neurodevelopmental or neurofunctional outcome, 11% had delays in all domains, and 6% remained severely delayed.

**HEARING IMPAIRMENT**

Hearing impairment, mainly sensorineural hearing loss (SNHL) can be viewed as another type of neurodevelopmental complication. SNHL appears to be a progressive phenomenon; with reported incidences between 0% to 100%[24,33-42]. In a recent report, Partridge and associates[37] followed 112 CDH patients. Interestingly, SNHL was found in approximately 3%, a rate comparable to the prevalence of SNHL in graduates from neonatal intensive care units for other problems (2%-6%). Unexpectedly, they found a high incidence (34%) of abnormalities in auditory brainstem response and/or behavioral audiometry consistent with conductive hearing loss.

Although hearing impairment in CDH has been attributed to a number of risk factors, the pathophysiology remains poorly understood. For example, need for ECMO, severe hypoxia, acidosis, duration of mechanical ventilation and NICU stay, and the prolonged exposure to ototoxic drugs have all been reported as risk factors[24, 33-37]. Furthermore, genetic predisposition to hearing loss and cumulative noise exposure have also been postulated as potential causes of SNHL in CDH patients. Additional studies are necessary to define their role in the CDH population. In general, infants with hearing impairment are at increased risk for delayed language acquisition, poor social development, and impaired academic achievement. Early identification and appropriate intervention may be critical in minimizing adverse effects and optimizing developmental outcomes.

**QUALITY OF LIFE**

Although, quality of life (QoL) assessment has emerged as an essential outcome measurement in many high-risk patient populations (*e.g.*, congenital heart disease, extremely low-birth weight children), few studies have evaluated QoL in the CDH population. Poley *et al*[13] studied 111 CDH children. Preschool CDH patients had lower scores in five of the thirteen domains tested. Adolescents demonstrated considerable deficits in several areas of every day functioning. No differences were found between young CDH adults and the control population.

In a study of 69 adults with CDH, Koivusalo *et al*[43] found lower QoL scores and the frequency of attaining higher educational levels (*e.g.*, college) in 25% of the study population. Bouman *et al*[29] assessed the emotional outcomes and that 36% of CDH children may have depressive problems.

Chen *et al*[44] studied the QoL of 53 CDH children at a median age of 8 years and found that ongoing clinical problems translated into lower functional status, particularly in overall general health and interpersonal functioning. Further research is warranted to delineate associations between specific aspects of neurodevelopmental outcome and QoL and to identify neurologic impairments that may be improved through early intervention. By characterizing the relationship between disease complexity, neurodevelopmental morbidity, and QoL, health care professionals and caregivers may be able to significantly improve the lives of CDH children and ensure their future success.

**RISK FACTORS FOR ADVERSE NEUROLOGICAL OUTCOME**

Based on the available outcome data, various risk factors for adverse neurodevelopmental sequelae have been identified[8,9,12,23-25,31,32,45]. For example, position of the liver one of the most important factors of survival. In one of the largest series of isolated left-sided CDH patients, Hedrick *et al*[2] demonstrated that neonates with intrathoracic liver position had a mortality of approximately 55% and 80% required ECMO. Of note, Danzer *et al*[12] reported that more than two-thirds of CDH children with prenatally diagnosed intrathoracic liver position had delayed neurodevelopmental function.

Several studies have reported a survival advantage of right-sided CDH compared to left-sided defects[46,47]. This improved survival of right CDH children must be cautioned by a high prevalence of associated problems, suggesting that the higher incidence of neurologic deficits these children may be in part due to the survival of extremely sick right CDH patients.

The need for ECMO is associated higher risk of neurological impairments[12,14,23,27-29,35,48,49]. Whether the increased incidence of adverse outcome associated with ECMO indicates a more severe form of CDH or a reflection of ECMO-associated complications continues to be under discussion. In general ECMO is reserved for the sickest newborns[50,51]. ECMO therapy may also be linked to neurological impairments due to the need for anticoagulative therapy, development of intracranial hemorrhage, and alteration of intracranial blood flow secondary to the necessary ligation of the carotid artery. The type of ECMO modality used may impact function. Historically, venoarterial (VA) ECMO has been used. Recent studies suggest that venovenous (VV) ECMO may be as useful as VA ECMO with a lower prevalence of sequelae[52,53].

The need for a patch to repair the diaphragm or the need for oxygen beyond 30 days may also play and important role in neurological outcome[17,23,24,46].

In addition to the above mentioned potentially modifiable predictors, many independent risk factors of adverse neurodevelopmental outcome are not modifiable, such as innate patient-related variables, including associated malformations, genetic syndromes, the higher than expected incidence of autism and autism spectrum disorder[17]. The apparent link between CDH and autism spectrum risk is of concern. If more CDH children are diagnosed with autism in the future, one should consider including them as part of outcomes. Moreover, parental education and social-economic status, which are also not modifiable factors, are also associated with adverse outcome. Stolar *et al*[53] reported that low-level maternal education correlates with the incidence of delays. Wynn *et al*[26] expanded on these initial findings and showed that not only maternal education, but also paternal education and household income less than $30000 were associated with lower neurodevelopmental and functional scores.

**PATHOPHYSIOLOGIC MECHANISM**

While the abovementioned predictors support the concept that disease severity correlates with the severity of neurodevelopmental problems, the mechanisms remain poorly understood. Several reports suggest that children with CDH have a higher incidence of cerebral abnormalities than the general population[54-57]. Hunt *et al*[55] found a disturbingly high incidence of brain abnormalities in CDH newborns on postnatal magnetic resonance imaging (MRI) studies. Danzer *et al*[56] found that the development of the brain in CDH neonates might be delayed. They also found that 18% of infants studied had periventricular leukomalacia, as well as delayed closure of the cerebral opercula in 14%. Although the etiology of central nervous system injury in CDH patients is almost certainly multifactorial, changes in cerebral circulation are common and appear to play a pivotal role[56]. In normal fetal brain development, the formation of the cerebral cortex begins at about 6 wk gestation with the formation of the ventricular zone of the dorsal and ventral germinal matrixes, followed by a well-orchestrated sequence of structural changes including the gradual appearance of deep primary and more superficial secondary cortical infolding, neuronal migration and arborization, synaptogenesis, programmed cell death, oligodendrocyte maturation, and extensive reorganization of synaptic connections during the second half of gestation[58-63]. Beginning in the third trimester, myelination of the cerebral hemispheres accelerates[64,65]. These important processes during fetal brain development place an escalating demand on the cardiopulmonary system for delivery of oxygenated blood. The observed brain abnormalities in CDH might be in part caused by prolonged impairment of cerebral oxygen delivery. Of note, in children with congenital heart defects, the brain receives lower levels of oxygen-saturated blood from the right ventricle as a consequence of disordered fetal circulation[66,67]. In CDH fetuses, the left ventricle is one-third smaller and the left ventricular output is reduced[68-70]. These alterations may affect cerebral perfusion and compromise cerebral development. Of note, Buesing *et al*[71] showed that cerebral blood flow is altered in CDH survivors[71,72]. In addition to a prenatal insult, CDH neonates are exposed to the potential risk of hypoxia/ischemia, emboli, reactive oxygen species, acidosis, neuro-modulating drugs and inflammatory microvasculopathy before and after surgery, all of which may affect the white matter maturation and in turn neurodevelopment[59,63,73-77].

**CONCLUSION**

Infants and children with CDH often have significant neurodevelopmental and neurofunctional sequelae compared with population norms. Some of the identified early developmental abnormalities may improve over time. Identifying deficits early and providing early physical, occupational, and academic interventions may help to improve neurological morbidities before additional disabilities evolve and optimize long-term academic achievements. The American Academy of Pediatrics[18] has established follow-up guidelines for CDH survivors after discharge to highlight the importance of monitoring the developmental problems in this high-risk population throughout infancy and childhood.

Future research should focus on intervention strategies that not only reduce the pulmonary sequelae in CDH, but also in improving prenatal hemodynamics and cerebral blood flow to optimize brain development and improve outcome. Further, robust and longitudinal studies that incorporate advanced neuroimaging techniques and comprehensive assessments are warranted to further improve outcomes in CHD survivors.

**REFERENCES**

1 **Hedrick HL**. Management of prenatally diagnosed congenital diaphragmatic hernia. *Semin Pediatr Surg* 2013; **22**: 37-43 [PMID: 23395144 DOI: 10.1053/j.sempedsurg.2012.10.007]

2 **Hedrick HL**, Danzer E, Merchant A, Bebbington MW, Zhao H, Flake AW, Johnson MP, Liechty KW, Howell LJ, Wilson RD, Adzick NS. Liver position and lung-to-head ratio for prediction of extracorporeal membrane oxygenation and survival in isolated left congenital diaphragmatic hernia. *Am J Obstet Gynecol* 2007; **197**: 422.e1-422.e4 [PMID: 17904987]

3 **Chiu P**, Hedrick HL. Postnatal management and long-term outcome for survivors with congenital diaphragmatic hernia. *Prenat Diagn* 2008; **28**: 592-603 [PMID: 18551724 DOI: 10.1002/pd.2007]

4 **Peetsold MG**, Kneepkens CM, Heij HA, IJsselstijn H, Tibboel D, Gemke RJ. Congenital diaphragmatic hernia: long-term risk of gastroesophageal reflux disease. *J Pediatr Gastroenterol Nutr* 2010; **51**: 448-453 [PMID: 20512059 DOI: 10.1097/MPG.0b013e3181d1b149]

5 **Peetsold MG**, Heij HA, Kneepkens CM, Nagelkerke AF, Huisman J, Gemke RJ. The long-term follow-up of patients with a congenital diaphragmatic hernia: a broad spectrum of morbidity. *Pediatr Surg Int* 2009; **25**: 1-17 [PMID: 18841373 DOI: 10.1007/s00383-008-2257-y]

6 **Jancelewicz T**, Vu LT, Keller RL, Bratton B, Lee H, Farmer D, Harrison M, Miniati D, Mackenzie T, Hirose S, Nobuhara K. Long-term surgical outcomes in congenital diaphragmatic hernia: observations from a single institution. *J Pediatr Surg* 2010; **45**: 155-60; discussion 160 [PMID: 20105597 DOI: 10.1016/j.jpedsurg.2009.10.028]

7 **Chiu PP**, Sauer C, Mihailovic A, Adatia I, Bohn D, Coates AL, Langer JC. The price of success in the management of congenital diaphragmatic hernia: is improved survival accompanied by an increase in long-term morbidity? *J Pediatr Surg* 2006; **41**: 888-892 [PMID: 16677876 DOI: 10.1016/j.jpedsurg.2006.01.026]

8 **Nobuhara KK**, Lund DP, Mitchell J, Kharasch V, Wilson JM. Long-term outlook for survivors of congenital diaphragmatic hernia. *Clin Perinatol* 1996; **23**: 873-887 [PMID: 8982576]

9 **Lund DP**, Mitchell J, Kharasch V, Quigley S, Kuehn M, Wilson JM. Congenital diaphragmatic hernia: the hidden morbidity. *J Pediatr Surg* 1994; **29**: 258-62; discussion 262-4 [PMID: 8176602 DOI: 10.1016/0022-3468(94)90329-8]

10 **Danzer E**, Gerdes M, D'Agostino JA, Hoffman C, Bernbaum J, Bebbington MW, Siegle J, Sulkowski J, Rintoul NE, Flake AW, Scott Adzick N, Hedrick HL. Longitudinal neurodevelopmental and neuromotor outcome in congenital diaphragmatic hernia patients in the first 3 years of life. *J Perinatol* 2013; **33**: 893-898 [PMID: 23660581 DOI: 10.1038/jp.2013.47]

11 **Danzer E**, Gerdes M, D'Agostino JA, Partridge EA, Hoffman-Craven CH, Bernbaum J, Rintoul NE, Flake AW, Adzick NS, Hedrick HL. Preschool neurological assessment in congenital diaphragmatic hernia survivors: outcome and perinatal factors associated with neurodevelopmental impairment. *Early Hum Dev* 2013; **89**: 393-400 [PMID: 23333410 DOI: 10.1016/j.earlhumdev.2012.12.009]

12 **Danzer E**, Gerdes M, Bernbaum J, D'Agostino J, Bebbington MW, Siegle J, Hoffman C, Rintoul NE, Flake AW, Adzick NS, Hedrick HL. Neurodevelopmental outcome of infants with congenital diaphragmatic hernia prospectively enrolled in an interdisciplinary follow-up program. *J Pediatr Surg* 2010; **45**: 1759-1766 [PMID: 20850617 DOI: 10.1016/j.jpedsurg.2010.03.011]

13 **Poley MJ**, Stolk EA, Tibboel D, Molenaar JC, Busschbach JJ. Short term and long term health related quality of life after congenital anorectal malformations and congenital diaphragmatic hernia. *Arch Dis Child* 2004; **89**: 836-841 [PMID: 15321860 DOI: 10.1136/adc.2002.016543]

14 **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 [PMID: 7478834]

15 **Frisk V**, Jakobson LS, Unger S, Trachsel D, O'Brien K. Long-term neurodevelopmental outcomes of congenital diaphragmatic hernia survivors not treated with extracorporeal membrane oxygenation. *J Pediatr Surg* 2011; **46**: 1309-1318 [PMID: 21763827 DOI: 10.1016/j.jpedsurg.2010.12.023]

16 **Rasheed A**, Tindall S, Cueny DL, Klein MD, Delaney-Black V. Neurodevelopmental outcome after congenital diaphragmatic hernia: Extracorporeal membrane oxygenation before and after surgery. *J Pediatr Surg* 2001; **36**: 539-544 [PMID: 11283873 DOI: 10.1053/jpsu.2001.22278]

17 **Danzer E**, Gerdes M, D'Agostino JA, Bernbaum J, Siegle J, Hoffman C, Rintoul NE, Liechty KW, Flake AW, Adzick NS, Hedrick HL. Prospective, interdisciplinary follow-up of children with prenatally diagnosed giant omphalocele: short-term neurodevelopmental outcome. *J Pediatr Surg* 2010; **45**: 718-723 [PMID: 20385277 DOI: 10.1016/j.jpedsurg.2009.09.004]

18 **Gerdes M**, Solot C, Wang PP, Moss E, LaRossa D, Randall P, Goldmuntz E, Clark BJ, Driscoll DA, Jawad A, Emanuel BS, McDonald-McGinn DM, Batshaw ML, Zackai EH. Cognitive and behavior profile of preschool children with chromosome 22q11.2 deletion. *Am J Med Genet* 1999; **85**: 127-133 [PMID: 10406665 DOI: 10.1002/(SICI)1096-8628(19990716)85: 2<127: : AID-AJMG6>3.0.CO; 2-F]

19 **Hibbs A**, Evans JR, Gerdes M, Hunter JV, Cullen JA. Outcome of infants with bronchopulmonary dysplasia who receive extracorporeal membrane oxygenation therapy. *J Pediatr Surg* 2001; **36**: 1479-1484 [PMID: 11584392 DOI: 10.1053/jpsu.2001.27026]

20 **Tabbutt S**, Nord AS, Jarvik GP, Bernbaum J, Wernovsky G, Gerdes M, Zackai E, Clancy RR, Nicolson SC, Spray TL, Gaynor JW. Neurodevelopmental outcomes after staged palliation for hypoplastic left heart syndrome. *Pediatrics* 2008; **121**: 476-483 [PMID: 18310195 DOI: 10.1542/peds.2007-1282]

21 **DeMauro SB**, D'Agostino JA, Bann C, Bernbaum J, Gerdes M, Bell EF, Carlo WA, D'Angio CT, Das A, Higgins R, Hintz SR, Laptook AR, Natarajan G, Nelin L, Poindexter BB, Sanchez PJ, Shankaran S, Stoll BJ, Truog W, Van Meurs KP, Vohr B, Walsh MC, Kirpalani H. Developmental outcomes of very preterm infants with tracheostomies. *J Pediatr* 2014; **164**: 1303-10.e2 [PMID: 24472229 DOI: 10.1016]

22 **Van Meurs KP**, Robbins ST, Reed VL, Karr SS, Wagner AE, Glass P, Anderson KD, Short BL. Congenital diaphragmatic hernia: long-term outcome in neonates treated with extracorporeal membrane oxygenation. *J Pediatr* 1993; **122**: 893-899 [PMID: 8501565 DOI: 10.1016/S0022-3476(09)90013-0]

23 **D'Agostino JA**, Bernbaum JC, Gerdes M, Schwartz IP, Coburn CE, Hirschl RB, Baumgart S, Polin RA. Outcome for infants with congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation: the first year. *J Pediatr Surg* 1995; **30**: 10-15 [PMID: 7722808 DOI: 10.1016/0022-3468(95)90598-7]

24 **Cortes RA**, Keller RL, Townsend T, Harrison MR, Farmer DL, Lee H, Piecuch RE, Leonard CH, Hetherton M, Bisgaard R, Nobuhara KK. Survival of severe congenital diaphragmatic hernia has morbid consequences. *J Pediatr Surg* 2005; **40**: 36-45; discussion 45-6 [PMID: 15868556]

25 **Chen C**, Friedman S, Butler S, Jeruss S, Terrin N, Tighiouart H, Ware J, Wilson JM, Parsons SK. Approaches to neurodevelopmental assessment in congenital diaphragmatic hernia survivors. *J Pediatr Surg* 2007; **42**: 1052-106; discussion 1056 [PMID: 17560219 DOI: 10.1016/j.jpedsurg.2007.01.042]

26 **Wynn J**, Aspelund G, Zygmunt A, Stolar CJ, Mychaliska G, Butcher J, Lim FY, Gratton T, Potoka D, Brennan K, Azarow K, Jackson B, Needelman H, Crombleholme T, Zhang Y, Duong J, Arkovitz MS, Chung WK, Farkouh C. Developmental outcomes of children with congenital diaphragmatic hernia: a multicenter prospective study. *J Pediatr Surg* 2013; **48**: 1995-2004 [PMID: 24094947 DOI: 10.1016/j.jpedsurg.2013.02.041]

27 **Nijhuis-van der Sanden MW**, van der Cammen-van Zijp MH, Janssen AJ, Reuser JJ, Mazer P, van Heijst AF, Gischler SJ, Tibboel D, Kollée LA. Motor performance in five-year-old extracorporeal membrane oxygenation survivors: a population-based study. *Crit Care* 2009; **13**: R47 [PMID: 19341476 DOI: 10.1186/cc7770]

28 **van der Cammen-van Zijp MH**, Gischler SJ, Mazer P, van Dijk M, Tibboel D, Ijsselstijn H. Motor-function and exercise capacity in children with major anatomical congenital anomalies: an evaluation at 5 years of age. *Early Hum Dev* 2010; **86**: 523-528 [PMID: 20678870 DOI: 10.1016/j.earlhumdev.2010.06.014]

29 **Bouman NH**, Koot HM, Tibboel D, Hazebroek FW. Children with congenital diaphragmatic hernia are at risk for lower levels of cognitive functioning and increased emotional and behavioral problems. *Eur J Pediatr Surg* 2000; **10**: 3-7 [PMID: 10770239 DOI: 10.1055/s-2008-1072314]

30 **Tureczek I**, Caflisch J, Moehrlen U, Natalucci G, Bernet V, Latal B. Long-term motor and cognitive outcome in children with congenital diaphragmatic hernia. *Acta Paediatr* 2012; **101**: 507-512 [PMID: 22176276 DOI: 10.1111/j.1651-2227.2011.02567]

31 **Gischler SJ**, Mazer P, Duivenvoorden HJ, van Dijk M, Bax NM, Hazebroek FW, Tibboel D. Interdisciplinary structural follow-up of surgical newborns: a prospective evaluation. *J Pediatr Surg* 2009; **44**: 1382-1389 [PMID: 19573666 DOI: 10.1016/j.jpedsurg.2008.12.034]

32 **Friedman S**, Chen C, Chapman JS, Jeruss S, Terrin N, Tighiouart H, Parsons SK, Wilson JM. Neurodevelopmental outcomes of congenital diaphragmatic hernia survivors followed in a multidisciplinary clinic at ages 1 and 3. *J Pediatr Surg* 2008; **43**: 1035-1043 [PMID: 18558179 DOI: 10.1016/j.jpedsurg.2008.02.029]

33 **Jaillard SM**, Pierrat V, Dubois A, Truffert P, Lequien P, Wurtz AJ, Storme L. Outcome at 2 years of infants with congenital diaphragmatic hernia: a population-based study. *Ann Thorac Surg* 2003; **75**: 250-256 [PMID: 12537224 DOI: 10.1016/S0003-4975(02)04278-9]

34 **Robertson CM**, Cheung PY, Haluschak MM, Elliott CA, Leonard NJ. High prevalence of sensorineural hearing loss among survivors of neonatal congenital diaphragmatic hernia. Western Canadian ECMO Follow-up Group. *Am J Otol* 1998; **19**: 730-736 [PMID: 9831145]

35 **Davis PJ**, Firmin RK, Manktelow B, Goldman AP, Davis CF, Smith JH, Cassidy JV, Shekerdemian LS. Long-term outcome following extracorporeal membrane oxygenation for congenital diaphragmatic hernia: the UK experience. *J Pediatr* 2004; **144**: 309-315 [PMID: 15001933 DOI: 10.1016/j.jpeds.2003.11.031]

36 **Fligor BJ**, Neault MW, Mullen CH, Feldman HA, Jones DT. Factors associated with sensorineural hearing loss among survivors of extracorporeal membrane oxygenation therapy. *Pediatrics* 2005; **115**: 1519-1528 [PMID: 15930212 DOI: 10.1542/peds.2004-0247]

37 **Partridge EA**, Bridge C, Donaher JG, Herkert L, Grill E, Danzer E, Gerdes M, Hoffman-Craven CH, D'Agostino J, Berbaum JC, Rintoul NE, Peranteau PW, Flake AW, Adzick NS, Hedrick HL: Incidence and factors assocaited with sensorineural and conductive hearing loss among survivors of congenital diaphragmatic hernia. *J Pediatr Surg* 2014; In press [DOI: 10.1016/j.jpedsurg.2014.01.019]

38 **Masumoto K**, Nagata K, Uesugi T, Yamada T, Taguchi T. Risk factors for sensorineural hearing loss in survivors with severe congenital diaphragmatic hernia. *Eur J Pediatr* 2007; **166**: 607-612 [PMID: 17043841 DOI: 10.1007/s00431-006-0300-3]

39 **Morini F**, Capolupo I, Masi R, Ronchetti MP, Locatelli M, Corchia C, Bagolan P. Hearing impairment in congenital diaphragmatic hernia: the inaudible and noiseless foot of time. *J Pediatr Surg* 2008; **43**: 380-384 [PMID: 18280294 DOI: 10.1016/j.jpedsurg.2007.10.048]

40 **Morando C**, Midrio P, Gamba P, Filippone M, Sgrò A, Orzan E. Hearing assessment in high-risk congenital diaphragmatic hernia survivors. *Int J Pediatr Otorhinolaryngol* 2010; **74**: 1176-1179 [PMID: 20688402 DOI: 10.1016/j.ijporl.2010.07.00]

41 **Wilson MG**, Riley P, Hurteau AM, Baird R, Puligandla PS. Hearing loss in congenital diaphragmatic hernia (CDH) survivors: is it as prevalent as we think? *J Pediatr Surg* 2013; **48**: 942-945 [PMID: 23701764 DOI: 10.1016/j.jpedsurg.2013.02.007]

42 **Safavi A**, Synnes AR, O'Brien K, Chiang M, Skarsgard ED, Chiu PP. Multi-institutional follow-up of patients with congenital diaphragmatic hernia reveals severe disability and variations in practice. *J Pediatr Surg* 2012; **47**: 836-841 [PMID: 22595557 DOI: 10.1016/j.jpedsurg.2012.01.032]

43 **Koivusalo A**, Pakarinen M, Vanamo K, Lindahl H, Rintala RJ. Health-related quality of life in adults after repair of congenital diaphragmatic defects--a questionnaire study. *J Pediatr Surg* 2005; **40**: 1376-1381 [PMID: 16150336 DOI: 10.1016/j.jpedsurg.2005.05.037]

44 **Chen C**, Jeruss S, Chapman JS, Terrin N, Tighiouart H, Glassman E, Wilson JM, Parsons SK. Long-term functional impact of congenital diaphragmatic hernia repair on children. *J Pediatr Surg* 2007; **42**: 657-665 [PMID: 17448762 DOI: 10.1016/j.jpedsurg.2006.12.013]

45 **Lally KP**, Lally PA, Lasky RE, Tibboel D, Jaksic T, Wilson JM, Frenckner B, Van Meurs KP, Bohn DJ, Davis CF, Hirschl RB. Defect size determines survival in infants with congenital diaphragmatic hernia. *Pediatrics* 2007; **120**: e651-e657 [PMID: 17766505 DOI: 10.1542/peds.2006-3040]

46 **Hedrick HL**, Crombleholme TM, Flake AW, Nance ML, von Allmen D, Howell LJ, Johnson MP, Wilson RD, Adzick NS. Right congenital diaphragmatic hernia: Prenatal assessment and outcome. *J Pediatr Surg* 2004; **39**: 319-23; discussion 319-23 [PMID: 15017545 DOI: 10.1016/j.jpedsurg.2003.11.006]

47 **Fisher JC**, Jefferson RA, Arkovitz MS, Stolar CJ. Redefining outcomes in right congenital diaphragmatic hernia. *J Pediatr Surg* 2008; **43**: 373-379 [PMID: 18280293 DOI: 10.1016/j.jpedsurg.2007.10.049]

48 **McGahren ED**, Mallik K, Rodgers BM. Neurological outcome is diminished in survivors of congenital diaphragmatic hernia requiring extracorporeal membrane oxygenation. *J Pediatr Surg* 1997; **32**: 1216-1220 [PMID: 9269973 DOI: 10.1016/S0022-3468(97)90685-0]

49 **Davenport M**, Rivlin E, D'Souza SW, Bianchi A. Delayed surgery for congenital diaphragmatic hernia: neurodevelopmental outcome in later childhood. *Arch Dis Child* 1992; **67**: 1353-1356 [PMID: 1281972 DOI: 10.1136/adc.67.11.1353]

50 **Rothenbach P**, Lange P, Powell D. The use of extracorporeal membrane oxygenation in infants with congenital diaphragmatic hernia. *Semin Perinatol* 2005; **29**: 40-44 [PMID: 15921151 DOI: 10.1053/j.semperi.2005.02.006]

51 **Kugelman A**, Gangitano E, Pincros J, Tantivit P, Taschuk R, Durand M. Venovenous versus venoarterial extracorporeal membrane oxygenation in congenital diaphragmatic hernia. *J Pediatr Surg* 2003; **38**: 1131-1136 [PMID: 12891480 DOI: 10.1016/S0022-3468(03)00256-2]

52 **Dimmitt RA**, Moss RL, Rhine WD, Benitz WE, Henry MC, Vanmeurs KP. Venoarterial versus venovenous extracorporeal membrane oxygenation in congenital diaphragmatic hernia: the Extracorporeal Life Support Organization Registry, 1990-1999. *J Pediatr Surg* 2001; **36**: 1199-1204 [PMID: 11479856 DOI: 10.1053/jpsu.2001.25762]

53 **Stolar CJ**, Crisafi MA, Driscoll YT. Neurocognitive outcome for neonates treated with extracorporeal membrane oxygenation: are infants with congenital diaphragmatic hernia different? *J Pediatr Surg* 1995; **30**: 366-71; discussion 371-2 [PMID: 7537811 DOI: 10.1016/0022-3468(95)90591-X]

54 **Tracy S**, Estroff J, Valim C, Friedman S, Chen C. Abnormal neuroimaging and neurodevelopmental findings in a cohort of antenatally diagnosed congenital diaphragmatic hernia survivors. *J Pediatr Surg* 2010; **45**: 958-965 [PMID: 20438935 DOI: 10.1016/j.jpedsurg.2010.02.015]

55 **Hunt RW**, Kean MJ, Stewart MJ, Inder TE. Patterns of cerebral injury in a series of infants with congenital diaphragmatic hernia utilizing magnetic resonance imaging. *J Pediatr Surg* 2004; **39**: 31-36 [PMID: 14694367 DOI: 10.1016/j.jpedsurg.2003.09.005]

56 **Danzer E**, Zarnow D, Gerdes M, D'Agostino JA, Siegle J, Bebbington MW, Flake AW, Adzick NS, Hedrick HL. Abnormal brain development and maturation on magnetic resonance imaging in survivors of severe congenital diaphragmatic hernia. *J Pediatr Surg* 2012; **47**: 453-461 [PMID: 22424337 DOI: 10.1016/j.jpedsurg.2011.10.002]

57 **Ahmad A**, Gangitano E, Odell RM, Doran R, Durand M. Survival, intracranial lesions, and neurodevelopmental outcome in infants with congenital diaphragmatic hernia treated with extracorporeal membrane oxygenation. *J Perinatol* 1999; **19**: 436-440 [PMID: 10685274 DOI: 10.1038/sj.jp.7200242]

58 **Volpe JJ**. Neurobiology of periventricular leukomalacia in the premature infant. *Pediatr Res* 2001; **50**: 553-562 [PMID: 11641446 DOI: 10.1203/00006450-200111000-00003]

59 **Volpe JJ**. Brain injury in the premature infant--from pathogenesis to prevention. *Brain Dev* 1997; **19**: 519-534 [PMID: 9440796 DOI: 10.1016/S0387-7604(97)00078-8]

60 **ten Donkelaar HJ**. Major events in the development of the forebrain. *Eur J Morphol* 2000; **38**: 301-308 [PMID: 11151042 DOI: 10.1076/ejom.38.5.301.7356]

61 **Pilz D**, Stoodley N, Golden JA. Neuronal migration, cerebral cortical development, and cerebral cortical anomalies. *J Neuropathol Exp Neurol* 2002; **61**: 1-11 [PMID: 11829339]

62 **Haynes RL**, Billiards SS, Borenstein NS, Volpe JJ, Kinney HC. Diffuse axonal injury in periventricular leukomalacia as determined by apoptotic marker fractin. *Pediatr Res* 2008; **63**: 656-661 [PMID: 18520330 DOI: 10.1203/PDR.0b013e31816c825c]

63 **Haynes RL**, Borenstein NS, Desilva TM, Folkerth RD, Liu LG, Volpe JJ, Kinney HC. Axonal development in the cerebral white matter of the human fetus and infant. *J Comp Neurol* 2005; **484**: 156-167 [PMID: 15736232 DOI: 10.1002/cne.20453]

64 **Girard N**, Raybaud C, Gambarelli D, Figarella-Branger D. Fetal brain MR imaging. *Magn Reson Imaging Clin N Am* 2001; **9**: 19-56, vii [PMID: 11278182]

65 **Girard N**, Raybaud C, Poncet M. In vivo MR study of brain maturation in normal fetuses. *AJNR Am J Neuroradiol* 1995; **16**: 407-413 [PMID: 7726092]

66 **Kiserud T**. Physiology of the fetal circulation. *Semin Fetal Neonatal Med* 2005; **10**: 493-503 [PMID: 16236564 DOI: 10.1016/j.siny.2005.08.007]

67 **Gardiner HM**. Response of the fetal heart to changes in load: from hyperplasia to heart failure. *Heart* 2005; **91**: 871-873 [PMID: 15958350 DOI: 10.1136/hrt.2004.047399]

68 **VanderWall KJ**, Kohl T, Adzick NS, Silverman NH, Hoffman JI, Harrison MR. Fetal diaphragmatic hernia: echocardiography and clinical outcome. *J Pediatr Surg* 1997; **32**: 223-25; discussion 223-25 [PMID: 9044126 DOI: 10.1016/S0022-3468(97)90183-4]

69 **Allan LD**, Irish MS, Glick PL. The fetal heart in diaphragmatic hernia. *Clin Perinatol* 1996; **23**: 795-812 [PMID: 8982572]

70 **Van Mieghem T**, Gucciardo L, Doné E, Van Schoubroeck D, Graatsma EM, Visser GH, Verhaeghe J, Deprest J. Left ventricular cardiac function in fetuses with congenital diaphragmatic hernia and the effect of fetal endoscopic tracheal occlusion. *Ultrasound Obstet Gynecol* 2009; **34**: 424-429 [PMID: 19753655 DOI: 10.1002/uog.7340]

71 **Buesing KA**, Kilian AK, Schaible T, Loff S, Sumargo S, Neff KW. Extracorporeal membrane oxygenation in infants with congenital diaphragmatic hernia: follow-up MRI evaluating carotid artery reocclusion and neurologic outcome. *AJR Am J Roentgenol* 2007; **188**: 1636-1642 [PMID: 17515387 DOI: 10.2214/AJR.06.1319]

72 **Van Mieghem T**, Sandaite I, Michielsen K, Gucciardo L, Done E, Dekoninck P, Claus F, Deprest J. Fetal cerebral blood flow velocities in congenital diaphragmatic hernia. *Ultrasound Obstet Gynecol* 2010; **36**: 452-457 [PMID: 20521239 DOI: 10.1002/uog.7703]

73 **Perlman JM**. White matter injury in the preterm infant: an important determination of abnormal neurodevelopment outcome. *Early Hum Dev* 1998; **53**: 99-120 [PMID: 10195704 DOI: 10.1016/S0378-3782(98)00037-1]

74 **Rezaie P**, Dean A. Periventricular leukomalacia, inflammation and white matter lesions within the developing nervous system. *Neuropathology* 2002; **22**: 106-132 [PMID: 12416551 DOI: 10.1046/j.1440-1789.2002.00438.x]

75 **Folkerth RD**, Haynes RL, Borenstein NS, Belliveau RA, Trachtenberg F, Rosenberg PA, Volpe JJ, Kinney HC. Developmental lag in superoxide dismutases relative to other antioxidant enzymes in premyelinated human telencephalic white matter. *J Neuropathol Exp Neurol* 2004; **63**: 990-999 [PMID: 15453097]

76 **Ikonomidou C**, Bittigau P, Koch C, Genz K, Hoerster F, Felderhoff-Mueser U, Tenkova T, Dikranian K, Olney JW. Neurotransmitters and apoptosis in the developing brain. *Biochem Pharmacol* 2001; **62**: 401-405 [PMID: 11448448 DOI: 10.1016/S0006-2952(01)00696-7]

77 **Felderhoff-Mueser U**, Ikonomidou C. Mechanisms of neurodegeneration after paediatric brain injury. *Curr Opin Neurol* 2000; **13**: 141-145 [PMID: 10987570 DOI: 10.1097/00019052-200004000-00005]

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