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Congenital Diaphragmatic Hernia

In this Issue...

Congenital diaphragmatic hernia (CDH) is a relatively common birth defect associated with high mortality and long-term morbidity. Significant progress in better medical management has been made in the past 10 years. The most pressing issues that we continue to face include the need to better predict clinical course and outcome, the development of better post-natal and possibly pre-natal therapies, and the ability to understand the heterogeneity and etiology of these defects.

In this issue, we review recent data about current approaches to the genetics of diaphragmatic hernia; the prediction of outcome based on the lung size; techniques to estimate fetal lung volumes; the response of the lung to fetal endoscopic tracheal occlusion (FETO); and, as the utility of exogenous surfactant in CDH neonates continues to be a controversial topic, a recent study using human and animal models.

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Guest Faculty Disclosure

Kate G. Ackerman, MD has indicated that she has not received financial support for consultation, research, or evaluation and does not have financial interest relevant to this literature review.

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The author has indicated that there will be reference to unlabeled or unapproved uses of drugs, products, or procedures in this presentation.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be able to:

- Describe current investigations into the genetic contribution to human diaphragmatic defects
- Summarize the rationale for not supplementing CDH neonates with exogenous surfactant
- Discuss research into endoscopic tracheal occlusion to promote fetal lung growth

DECEMBER PODCAST



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In this audio interview with Kate G. Ackerman, MD, an Assistant Professor of Pediatrics and Biomedical Genetics in the Division of Pediatric Critical Care at the University of Rochester in Rochester, NY she discusses the pathophysiology of diaphragmatic defects and pulmonary hypoplasia, treatment options, and the genetic pathways that lead to the development of diaphragmatic defects.

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COMMENTARY

CDH is a relatively common birth defect, and long-term healthy survival in affected fetuses is low.¹ For this reason, many avenues of investigation into improving outcome are warranted. These include investigations into the mechanisms of development, as well as research to develop new ways to better predict outcome and to reduce morbidity and mortality. One approach to determining the cause of these defects is to investigate the genetic contribution to the disease. Recent

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advances have been made in determining multiple genetic contributors to the spectrum of diaphragmatic defects.² The articles by Scott et al and Slavotinek et al (reviewed herein) describe the use of whole genome array hybridization screens to identify cytogenetic hot spots for CDH patients. Specific chromosomal deletions are repeatedly associated with syndromic forms of CDH.^{3,4} Isolated CDH also has a genetic component supported by mouse models and by human association, but a single common genetic cause for CDH has not yet been identified.^{2,5}

Estimates of fetal lung size have been used to predict outcome in fetuses with CDH. Use of the lung area to head circumference ratio (LHR) to predict outcome has been used with mixed success. Since many variables affect the LHR measurement, it is difficult to compare data across centers or to determine why this measurement is not effective for all neonates.⁶ In Europe, FETO is used to promote lung growth in fetuses with high-risk CDH.⁷ As synopsised herein, Peralta et al describe the use of 3D ultrasound to show that lung volume increases after the procedure, and the increase in lung volume is associated with better outcome.⁸

Measurement of lung volume by fetal magnetic resonance imaging (MRI) has been developed as an alternative to ultrasound. The articles by Barnewolt et al and Hayakawa et al found that there was good risk prediction of survival based on fetal lung volume MRI. Although different measurement and calculation parameters were used, there was agreement in the ability to predict outcome.^{9,10} Perhaps lung volume MRI will be a better predictive tool than lung ultrasound across centers. Prediction of outcome might also be possible based on the size of the diaphragmatic defect. In the article from The Congenital Diaphragmatic Hernia Study Group, it was determined that the size of the defect at the time of repair was associated with the degree of morbidity and mortality.¹¹ It is still to be determined whether the defect size correlates well with lung size or whether hernia sizes can be measured in utero.

There has been previous debate about surfactant deficiency in neonates with CDH, largely based on findings of surfactant deficiency in a large animal model of CDH.¹² Boucherat et al studied surfactant maturation in human fetal lungs in fetuses with and without CDH and compared these findings to those in the sheep model. They found that human CDH fetal lungs had normal surfactant maturation and content, and that the sheep fetal measurements were different from humans.¹² This supports not using surfactant therapy in term neonates with CDH, and highlights the difficulty in assuming a mechanically generated animal model of CDH matches that of the human disease.

Overall, much progress has been made recently towards stratifying risk factors in the heterogeneous group of patients categorized as having "CDH". Hopefully, a future understanding of the basis for variability in lung size, defect size and type, and cardiopulmonary function in CDH patients will lead to the development of therapies to further improve outcome.

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GENETIC ETIOLOGY OF CONGENITAL DIAPHRAGMATIC DEFECTS

Scott DA, Klaassens M, Holder AM, et al. **Genome-wide oligonucleotide-based array comparative genome hybridization analysis of non-isolated congenital diaphragmatic hernia**. *Hum Mol Genet.* 2007;16(4):424-30.

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Slavotinek AM, Moshrefi A, Davis R, et al. **Array comparative genomic hybridization in patients with congenital diaphragmatic hernia: mapping of four CDH-critical regions and sequencing of candidate genes at 15q26.1-15q26.2**. *Eur J Hum Genet.* 2006;14(9):999-1008.

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CDH is considered a heterogeneous and complex birth defect, but association with specific mutations in genes has only been established in rare cases. In an attempt to identify genetic deletions that are associated with CDH, multiple groups have used recently developed technology to identify deletions that are smaller than those detected by standard chromosome analysis. Scott et al screened 26 patients with CDH and additional anomalies (CDH+), while Slavotinek investigated 29 patients with either isolated CDH (n=13) or CDH+ (n=16). Both studies used array comparative genomic hybridization techniques; regions of deletion or duplication were then refined and verified using fluorescence in-situ hybridization, microsatellite markers, or quantitative polymerase chain reaction. Both studies also performed sequence analysis of candidate genes known to be in the 15q26 CDH cytogenetic hot spot.

There were no significant chromosomal anomalies detected in Slavotinek's 13 patients with isolated CDH. In the combined group (both studies) with CDH+ (n=42), 11 significant deletions and/or duplications were detected. Of these, 3 significant changes that were not detected by standard G-banded chromosome analysis. The major cytogenetic regions identified by these groups (and others in previous publications) are in the 15q26, 8p23, 4p16, 11q, and 1q41 regions. New regions associated with CDH+ patients were identified on chromosome 6p, 14q, and 2q. Sequence analysis of genes located in the 15q26 critical region in a larger group of CDH patients did not reveal significant coding mutations in the nuclear hormone receptor gene COUP-TFII/NR2F2 (n=173 patients from both groups) or in the SIAT8B, CHD2, MCTP2, ARRDC4, or RGMA (n=100 patients) genes.

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Performing high-density whole genome arrays in children with CDH plus additional anomalies appears to be a viable technique for identifying new deletions or duplications associated with these defects. These techniques can identify changes that are not detected using routine G-banded chromosome analysis. From these, and other similar studies, we now have a list of CDH cytogenetic hot spots, and the hope is that these regions contain genes important for diaphragm development. Unfortunately, re-sequencing of the coding regions in the best candidate genes in children with CDH has not been revealing. Because chromosomal abnormalities may occur in up to 30% of patients with CDH, a genetics consultation is recommended for these patients.

SURFACTANT CONTENT IN CDH ASSOCIATED PULMONARY HYPOPLASIA

Boucherat O, Benachi A, Chailley-Heu B, et al. **Surfactant maturation is not delayed in human fetuses with diaphragmatic hernia.** *PLoS Med.* 2007;4(7):e237.

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The debate about whether the lungs of neonates with CDH are surfactant deficient stems from the reports of surfactant deficiency in large animal models of CDH. The finding of surfactant deficiency would support using surfactant therapy for CDH babies. The investigators collected autopsy material from 16 human fetuses (ages 22 weeks - 27 weeks post-conceptual age) diagnosed with CDH. Samples from the lungs of fetuses with CDH were compared to age-matched lungs from fetuses that died with non-pulmonary related diseases. Lungs that were ipsilateral to the hernia were used for analysis. Lung samples were also collected from the most common large animal model of CDH, that of surgical creation of a diaphragmatic hernia (sDH) in the sheep (ovine model). In this model, a hernia was created surgically in a lamb at 85d gestation, and the lamb was returned to the uterus until delivery by cesarean section at 139d gestation (full term = 145d). These lambs developed pulmonary hypoplasia similar in appearance to human fetuses with CDH. The sDH group had 3 cohorts: sDH without treatment (n=5), sDH with treatment by tracheal occlusion (n=3), and a control group with a sham surgery (n=6). Lungs from humans were evaluated for surfactant protein and lipid content (DSPC, PC, and surfactant proteins A, B, C, D), thyroid transcription factor (TTF-1), and growth factors keratinocyte growth factor (KGF), leptin, and neuregulin 1 beta 1 (NRG1- β 1), while sheep lungs were only evaluated for growth factor levels.

Overall, the investigators found no differences in surfactant protein or phospholipid concentration between human CDH lungs and normal fetal lungs. The authors found that DSPC and DSPC/PC phospholipid ratios increased exponentially with fetal age in both groups when normalized to either lung wet weight or lung DNA content. Surfactant proteins A-D measured in lungs from fetuses at 28-37 weeks gestation (n=6 from each group) were also the same between groups. TTF1 was also measured (as it is a positive regulator of surfactant protein gene promoter activity and an important transcription factor for lung development) - the investigators found no differences in TTF1 levels between groups. Finally, growth factors important for the maturation of surfactant containing alveolar type II cell [KGF], leptin, and [NRG1- β 1] were measured in both human fetal lung and in lung from the surgical ovine CDH model with and without tracheal occlusion. The assays for measurement of growth factors were different between groups (protein in humans, mRNA in sheep).

The authors found that there were no differences in leptin or NRG1- β 1 in the human groups, while KGF increased with age in CDH lungs after 22 weeks rather than decreased with gestational age as it did in controls. In sheep, however, KGF was decreased in the sDH group, and these levels were partially restored by tracheal occlusion (TO). Leptin levels did not change in sDH lung, but were increased with sDH + TO, while NRG (not necessarily specific NRG1- β 1) decreased 42% in the sDH group but was normal in the sDH + TO group.

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The investigators concluded that surfactant accumulation is normal in fetal CDH lungs. Although using fetal lung autopsy tissue has some limitations and could represent an unusually severe and heterogeneous group of CDH patients, the study showed (using multiple parameters) that alveolar cell maturation and production of surfactant protein and phospholipid was not different in CDH fetal lung when normalized for lung size. Since this finding is different from reports in the lung of the surgical sheep model of CDH, a comparison of surfactant control or modulating genes was done in human fetal CDH lung vs. sheep fetal CDH lung. The authors determined that these growth factors were modulated differently in the surgically-induced pulmonary hypoplasia and/or tracheal occlusion lung stretch model. This finding provides further evidence that a cautious approach is necessary when using the surgically induced model of pulmonary hypoplasia to study the biology of human CDH associated pulmonary hypoplasia.

DIAPHRAGM DEFECT SIZE PREDICTS OUTCOME

Congenital Diaphragmatic Hernia Study Group, Lally KP, Lally PA, Lasky RE, et al. **Defect size determines survival in infants with congenital diaphragmatic hernia.** *Pediatrics.* 2007;120(3):e651-7.

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The Congenital Diaphragmatic Hernia Study Group conducted a large prospective multicenter study (51 centers from 7 countries, 3062 infants) to investigate factors thought to influence death, including birth weight, Apgar scores, size of the diaphragmatic defect, and associated anomalies. The population studied was live born infants with congenital diaphragmatic hernia who received treatment at tertiary care centers between the years 1995-2004. The end points evaluated included survival to hospital discharge, duration of mechanical ventilation, and length of hospital stay. The size of the congenital diaphragmatic defect was determined by the operating surgeon and categorized as either agenesis or no agenesis; the patients without diaphragmatic agenesis were then categorized as having either large defects (patch required for repair) or small defects (primary repair, or closure with sutures not requiring a patch). Agenesis was defined as the lack of most of the diaphragm and included patients who lacked diaphragmatic rim muscle and/or who required a patch to be sutured to the ribs anteriorly and posteriorly. A fourth group of patients had no systematic evaluation of defect size because they did not have surgery. This group had fatal pulmonary hypoplasia and/or other severe congenital anomalies or chromosomal anomalies.

The overall survival in this cohort of live born CDH patients was 69%; however the survival rate if the defect was surgically repaired was 83%, reflecting the severity of the patients who were not repaired either because of severe congenital or chromosomal anomalies (28%) or those determined to be non-salvageable based on the degree of hemodynamic and/or respiratory insufficiency. Defect size was not formally evaluated in this group, but the authors noted that 50 of the 538 patients had available autopsy data, and that 68% of this group had diaphragm agenesis. In the patients who had surgery, and therefore an evaluation of defect size, multiple variables had some affect on survival (odds ratio [OR] for risk of death 1.25-2.95 reported for birth outside tertiary care facility, low birth weight, gestational age less than 37 weeks, or prenatal diagnosis). The presence of major cardiac anomalies or low Apgar scores had a moderate affect on survival (OR for risk of death with these variables 2.01-8.77). However, the investigators found the largest predictor of survival was the size of the diaphragmatic defect. Patients with diaphragmatic agenesis had a risk of death that was 14.07 (95% CI 10.35-19.13) times that of patients with primary repair, while the odds for risk of death were 5.04 (95%CI 3.71-6.86) if there was a large defect (not large enough to classify as agenesis) requiring a patch.

In summary, the size of the diaphragmatic defect correlates with mortality and morbidity in live born infants with congenital diaphragmatic hernia, and this factor may have a much larger impact than other known risk factors. The authors



hypothesize that the defect size is likely to be a marker for the degree of pulmonary hypoplasia. Major issues to be addressed in the future include the validation of this hypothesis in humans, the determination of defect size in the fetus, and the discovery of developmental mechanisms that result in a large vs a small defect size.

ENDOSCOPIC TRACHEAL OCCLUSION AND LUNG GROWTH

Peralta CF, Jani JC, Van Schoubroeck D, et al. **Fetal lung volume after endoscopic tracheal occlusion in the prediction of postnatal outcome.** *Am J Obstet Gynecol.* 2007 Sep 7; [Epub ahead of print]

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Predicting the severity of a fetus with CDH is important in that it helps in the decision to pursue in utero therapies, as well as prepares the family and medical staff for the perinatal course. In Europe, the FETO procedure is being performed on high-risk fetuses with CDH. This procedure involves in utero occlusion of the fetal trachea with an endoscopically placed detachable balloon. Occlusion of the trachea during lung development is associated with lung stretch and growth. In this study, a group performing FETO procedures investigated whether they could measure increased lung volumes with 3D ultrasound after FETO, and whether the degree of increase in lung volume was predictive of postnatal outcome.

Data were reported for 30 of 58 high-risk isolated CDH fetuses treated with FETO from 2002-2006. To meet study criteria, these fetuses had to have 3D ultrasound imaging data available of the lung contralateral to the hernia before, 2 days after, and 7 days after the procedure. In addition, they had to have had death attributed to pulmonary hypoplasia, pulmonary hypertension, or have had discharge from the hospital. High-risk CDH patients were defined as those having an LHR below 1.0 with liver herniated into the chest. Most cases had left-sided hernias (26 of 30). Lung volumes were compared to percentage of the appropriate mean for gestation (observed/expected lung volume x 100) for normal fetuses (previously collected from 650 normal fetuses at 12-32 weeks).

The authors found that all of the CDH initial contralateral lung volumes were below 60% of expected normal mean for gestation. Initial lung volumes in the group that survived to discharge were 21-59% of predicted, while those in patients who died with pulmonary hypoplasia or pulmonary hypertension were 13-38% predicted. At 7 days after FETO, survivor median lung volumes were 75% predicted (range 56-150%) while non-survivor median lung volumes were 52% predicted (range 30-68%). These observed-to-expected lung volume ratios were predictive of survival ($p < 0.001$), while other variables such as gestational age at FETO, gestational age at balloon removal, and delivery age were not significantly associated with survival.

This is one of many studies from this group evaluating FETO for the treatment of high-risk CDH. This particular study reported the use of a new three-dimensional imaging technology to predict lung volumes both before and after lung stretch and growth associated with the FETO procedure. The investigators found an association between improved lung volumes after FETO and improved survival to hospital discharge. Although they measured lung volumes both 2 and 7 days after FETO, they hypothesize that the volume after 7 days is a better predictor of outcome, as it indicates whether the lung has undergone growth and not just an acute fluid induced stretch. While the value of FETO as a therapy is discussed in other publications, this article highlights current experience with FETO and lung growth modulation in Europe.

LUNG VOLUME MEASUREMENTS BY MRI TO PREDICT OUTCOME



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Barnewolt CE, Kunisaki SM, Fauza DO, Nemes LP, Estroff JA, Jennings RW. **Percent predicted lung volumes as measured on fetal magnetic resonance imaging: a useful biometric parameter for risk stratification in congenital diaphragmatic hernia.** *J Pediatr Surg.* 2007;42(1):193-197.

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Hayakawa M, Seo T, Itakua A, et al. **The MRI findings of the right-sided fetal lung can be used to predict postnatal mortality and the requirement for extracorporeal membrane oxygenation in isolated left-sided congenital diaphragmatic hernia.** *Pediatr Res.* 2007 Jul;62(1):93-97.

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The measurement of lung size by ultrasound and the calculation of LHR for prediction of CDH outcome have poor reproducibility across different centers. Limitations to this technique include variability in measurement and normalization techniques, and poor validation for right-sided defects. Because LHR has not provided good predictive data about outcome in all centers, some clinicians have started to also use magnetic resonance (MR) imaging to measure in utero lung volume in fetuses with CDH. In these two prospective studies, MR imaging of lungs from fetuses with CDH was performed and associated with outcomes, including the need for extracorporeal membrane oxygenation (ECMO), hospital length of stay, and survival to hospital discharge.

Data were presented for 17 (Barnewolt et al) and 21 (Hayakawa et al) singleton fetuses with isolated CDH. Most fetuses had left sided CDH, although 5 fetuses from the Barnewolt's group had right sided CDH. Both groups reported a percent predicted lung volume measurement. Because fetal growth of CDH patients is known to be variable in the late 2nd and entire 3rd trimester, the Barnewolt group normalized lung volume measurements to the fetal thoracic size. Their reported calculation was the percent of predicted bilateral lung volume (PPLV). The Hayakawa group reported a percent right fetal lung volume in left sided CDH (%RFLV), which was based on comparison to measurements of the right lung volume in 24 fetuses without CDH at different gestational ages.

Both groups found that fetal lung volume measurements were significantly associated with outcome. Although Barnewolt's group only had 14 live born patients (3 were terminated), they reported that a PPLV threshold of 15 was predictive of need for ECMO, that survival with a PPLV of less than 15 required prolonged ECMO and had a 40% survival rate, and that those patients with PPLV measurements of 15 or greater had 100% survival. Hayakawa's group reported outcome data for 21 live born infants. In this group, the %RFLV was significantly lower in non-survivors (18.5%, range 0.0-4.3) vs. 53.4% (range 32.4-66.6) for survivors ($p=0.0014$). The %RFLV was also significantly lower in infants that required ECMO. Using a %RFLV cutoff of 45%, the %RFLV predicted mortality with a sensitivity and specificity of 1.00 and 0.69, respectively, with a positive predictive value of 0.67, and a negative predictive value of 1.00. The group also associated the ability or lack of ability to visualize the right-sided lower lung lobe (in left sided CDH) on MRI with mortality. When they could visualize the right lower lobe, they called this "present pulmonary baseline". The pulmonary baseline was present in 38% ($n=3$) of non-survivors but 100% ($n=13$) of survivors.

In summary, MR imaging of the lungs in fetuses with CDH may have utility as a tool to predict survival and use of ECMO. Although measurement techniques and calculations differ, these two studies provide promising evidence that MR imaging may be more reproducible than measurements made by ultrasound across centers. However, these studies can not be extrapolated to the entire CDH population since they both excluded CDH patients who had additional anomalies and the Hayakawa group excluded patients with right-sided CDH. Hopefully, in the future, standardization of measurements for left and right sided CDH will be possible across multiple centers.

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This activity has been developed for neonatologists, NICU nurses and respiratory therapists working with neonatal patients. There are no fees or prerequisites for this activity.

Learning Objectives — [back to top](#)

At the conclusion of this activity, participants should be able to:

- Describe current investigations into the genetic contribution to human diaphragmatic defects

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- Summarize the rationale for not supplementing CDH neonates with exogenous surfactant
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