

Congenital diaphragmatic hernia – an update

Congenital diaphragmatic hernia (CDH) occurs in 1 in 2-5,000 live births in the UK and it is potentially lethal. Over 50% of infants with CDH have associated congenital anomalies. Variable survival figures have been reported. Innovative approaches are being adopted at the extremes of the condition. Effective management is dependent on a full understanding of the pathophysiology of CDH. This article reviews current knowledge, practice and options for the future.

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Key points

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1. CDH remains a condition with a significantly high mortality rate despite advances in neonatal care.
2. Prenatal detection of severe CDH and fetal surgical techniques are currently being evaluated.
3. The honeymoon period of 24-48hr preoperative stabilisation remains the mainstay of management.
4. There is an urgent need for multi-centered randomised controlled trials to evaluate the management techniques for severe CDH.
5. Follow-up in a multidisciplinary setting is paramount.

Congenital diaphragmatic hernia (CDH) can be one of the most clinically challenging neonatal conditions. It occurs in 1 in 2-5000 live births in the UK with no predominance between the sexes. Herniation of abdominal contents into the thorax occurs, however it is the concomitant pulmonary hypoplasia and pulmonary hypertension that can be fatal. CDH was first described as an incidental finding at postmortem in 1679 by Lazarus Riverius. The first successful repair of CDH in a neonate was achieved by Gross in 1946. Despite recent remarkable advances in perioperative neonatal care and surgical techniques, CDH remains a condition with a significantly high mortality rate (31-58%)¹⁻⁴. There is considerable debate about the effectiveness of different therapeutic options. In addition it is apparent that a number of interventions have been introduced without rigorous levels of evidence based medicine⁵⁻⁷. This paper aims to review the controversy and debate in the current management of CDH.

Anatomy and embryology

The diaphragm is a musculotendinous structure composed of a central tendon surrounded by a muscular periphery. Most diaphragmatic defects in CDH are posterolateral and 85-90% are left sided, with 10-20% having an hernial sac.

The pathogenesis of CDH is still unclear. Two theories exist both supported by animal experimental data. One describes CDH originating as a hole in the diaphragm which causes the pulmonary sequelae. The second theory suggests CDH results from an abnormal mesenchymal plate^{8,9} (FIGURE 1).

Pathophysiology

The pathophysiology of CDH relates chiefly to the pulmonary hypoplasia and pulmonary hypertension. There is a reduction of terminal bronchioles and alveolar volume. Pre-acinar arterioles have excessive musculature, alveolar arteries have a reduced diameter and both have an exaggerated response to hypoxia, hypercarbia and acidosis resulting in the persistent pulmonary hypertension¹⁰. Nitric oxide has a role in adjusting pulmonary tone, however studies have failed to show a deficiency in CDH. Surfactant deficiency and hence poor lung compliance has also been suggested, but again little evidence exists to support this theory¹¹.

Associated anomalies

The live born incidence of co-existent abnormalities is 40-50%^{6,12}. Cardiac defects occur along with trisomies^{13,18,21} neural tube defects, renal anomalies and duodenal atresia^{6,12}. Midline defects, genitourinary problems and syndromes such as Fryn's and Pentology of Cantrell have also been reported^{10,11}.

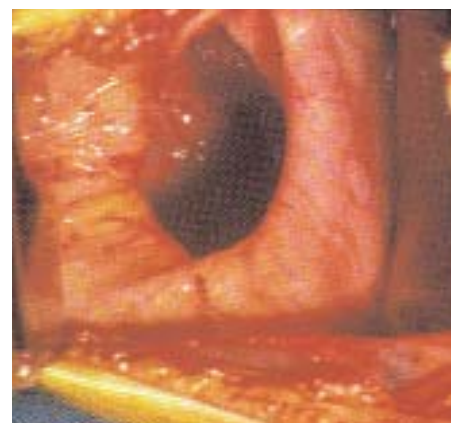


FIGURE 1 Incomplete formation of the diaphragm.

Genetics

At the 2006 CDH congress in Mannheim, the retinoic acid signalling pathway was highlighted as a point of focus¹³. Candidate genes including COUP-TF2, Slit 3 and FOG2 have been identified. However the aetiology is considered likely to be multifactorial with significant environmental effects.

Antenatal presentation

The majority of first presentations are made in the antenatal period. Diagnosis can be made with a 20 week maternal ultrasound scan and in some cases earlier. The scan can show polyhydramnios, an absent intra-abdominal gastric bubble, and mediastinal shift. However an accurate prediction of outcome is not possible at such an early stage.

Antenatal prognostic indicators

Ultrasound of lung volumes has suggested that 40-45% of normal volume is required for survival¹⁴. Lung area to head circumference ratio (LHR) with respect to gestation age has also been reported as a useful tool¹⁵, as has lung volume calculation by magnetic resonance imaging¹⁶. A retrospective ten centre study revealed a low LHR with herniation of the liver as predictive of non-survival¹⁷.

Fetoscopic tracheal occlusion (FETO)

In principle, antenatally diagnosed severe CDH, liver herniation and LHR < 0.9, may be considered for placement of a balloon to occlude the trachea at approximately 29-34 weeks' gestation. The balloon is left *in-situ* for 8-22 days and usually removed 1-2 weeks before delivery.

The initial trial of FETO in San Francisco in 24 cases failed. A pan-European trial is underway¹⁷. Preliminary results presented at the 2006 CDH update conference highlighted dramatic increases in lung volumes up to 118%, but decreasing to an average increase of 25% after removal¹⁸. However our understanding of human alveolar growth is not complete, and one must consider that alveolar enlargement without bronchiolar growth has the potential for good oxygenation, without optimal carbon dioxide removal, as in emphysema. There is also the question of the effect on pulmonary vascularity. The implications of the FETO studies, both ethically and the effect on survival, will be more apparent as the trial concludes.

Postnatal presentation

The majority of neonates presenting in the early postnatal period show a variety of clinical signs including respiratory distress, cyanosis, reduced breath sounds and shifting of the cardiac impulse.

Others include a scaphoid abdomen, presence of bowel sounds in the chest and radiological evidence of bowel loops within the thoracic cavity.

Approximately 5% present after 24 hours of age, with failure to thrive, recurrent chest infections, pleural effusions or incidentally on chest X-ray (**FIGURE 2**).

Initial postnatal management

Management may begin during the antenatal period with planned delivery at a regional neonatal unit and counselling for the parents. At planned deliveries immediate ventilation via an oral endotracheal tube is instigated. Face mask ventilation, that may cause gastric rupture or bowel distension and pneumothoraces, should be avoided if possible⁵. A nasogastric tube is inserted to deflate the stomach and intravenous sedation with or without paralysis is commenced. After initial stabilisation the child is transferred to a neonatal intensive care unit for further management. Cardiorespiratory support with pre and post ductal oxygen saturation and invasive blood pressure monitoring are instituted. The aims are to oxygenate, but avoid iatrogenic lung injury with so-called 'gentle ventilation', to minimise pulmonary hypertension and maintain cardiac output. Though not clearly defined, gentle ventilation would appear to keep peak inspiratory pressures below 30cm H₂O and allow permissive hypercapnia^{5,6}. It is felt that persistent pulmonary hypertension may be reduced by maintaining oxygenation, avoiding acidosis and hypothermia and minimal handling⁶. If this fails advanced techniques described below are initiated.



FIGURE 2 Bowel gas present in left hemithorax.

Prognostic indicators

The clinical severity can be assessed by the response to initial management and various indices. Positive indicators include a 'honeymoon period' of stability for about twenty four hours¹⁹, signs of an effective pulmonary circulation and conventional ventilation achieving a post ductal PaCO₂ of < 5.5KPa or a PaO₂ > 13 KPa²⁰⁻²⁵. Poor prognostic factors include antenatal diagnosis, gestation < 34 weeks, birth weight < 1.8kg, and the presence of other abnormalities. In addition, an alveolar-arterial DO₂ > 70 KPa, arterial pH < 7, PaCO₂ > 5.5 KPa on maximal conventional ventilation and an oxygen index > 40, are all signs of a high mortality 20-25.

Failure of conventional treatment

An oxygen index > 20 can be used to signal when conventional treatment is failing. Clinically this failure is seen by continued shunting, refractory pulmonary hypertension, the need for peak inspiratory pressures > 30 cmH₂O, 100% oxygen therapy, and the need for inotropes to support cardiorespiratory function²¹⁻²⁴. Despite increased availability of new treatment options over the last 20 years such as extracorporeal membrane oxygenation (ECMO) and nitric oxide, the mortality rate has shown little improvement^{5,12}. There is little high level evidence relating to therapies such as administration of surfactant, NO, HFOV,

ECMO, and treatments aimed at reducing pulmonary hypertension.

Prevention of right heart failure

In 2002 Kubota reported a decrease in ECMO requirement from 58% to 6% and an increase in survival from 42% to 94%²⁶. This was achieved by considering the changes at birth from the fetal circulation with CDH. It was postulated that a marked increase in right ventricular afterload after the ductus arteriosus (DA) closes, is a key factor leading to right ventricular failure and death. A combination of prostaglandin E₁ and nitric oxide was utilised to keep the DA open, in addition to attenuating pulmonary hypertension. A resultant decrease in right ventricular after load and improved systemic blood flow was reported to cause the marked increase in survival. Total pulmonary artery index [left + right diameter (mm) / body surface area (m²)] correlated well with survival and inversely with ventilator days²⁶.

Advanced ventilatory options

Surfactant

In normal healthy lung tissue surfactant is produced *in utero* by type 2 pneumocytes. Research has suggested that neonates with CDH have a relative deficiency of some components of surfactant and have a decreased overall concentration^{27, 28}. Animal studies have demonstrated that the prophylactic administration of surfactant is more effective than its delayed use in lambs with CDH²⁹.

Surfactant has been incorporated into treatment algorithms for patients with CDH worldwide, according to data published by the International CDH Registry and other individual researchers^{19, 30-33}. The data from the registry shows no increase in survival rates and a lack of clinical response for either preterm or term neonates with CDH, when given surfactant^{19, 30-33}. At present, there are no randomised controlled clinical trials to provide definitive evidence as to whether surfactant is beneficial in term neonates with CDH. The anecdotal work so far, suggests that there is no significant increase in survival with surfactant as a monotherapy.

High frequency oscillatory ventilation

This can be used as part of preoperative stabilisation or postoperative rescue treatment and is recommended for use in

neonates with hypercarbia and hypoxaemia resistant to conventional ventilation strategies³⁴. Gas exchange may be improved without increased ventilatory pressures and elimination of carbon dioxide decreases the stimulus for pulmonary vasoconstriction hence decreasing pulmonary hypertension. Direct alveolar ventilation may be achieved, allowing a decreased FiO₂, and providing a decreased A-aO₂ gradient.

Nitric oxide

This is a selective pulmonary vasodilator with an extremely short half life of 10 seconds, which therefore has only a minimal systemic effect. Nitric oxide exerts its vasodilatory effect via the cyclic guanosine monophosphate pathway and is inactivated by haemoglobin. It is administered in a dose of between 20-40ppm and is considered if the oxygen index >20 or there is obvious clinical evidence of shunting. The duration of treatment can be prolonged for days or weeks if indicated and monitoring of higher oxides of nitrogen and methaemoglobin is also required. It is thought to have a synergistic effect if administered with surfactant, but overall there have been variable reports regarding its benefits. The Neonatal Inhaled Nitric Oxide Study (NINOS) Group in 1997 showed no increase in survival rates in those babies with CDH who received nitric oxide³⁵. In addition nitric oxide did not reduce the need for ECMO.

Extracorporeal membrane oxygenation (ECMO)

ECMO was introduced into the UK in 1989; it is a technique for oxygenating blood outside the body, bypassing the need for gas exchange in the lungs and providing cardiovascular support if required. Airway pressure can be controlled at lower values, oxygen toxicity can be reduced, shunting can potentially be eliminated, and pulmonary blood flow can be reduced. ECMO can also facilitate gradual expansion of the lung tissue.

Stringent criteria for eligibility for ECMO exist and usually include an oxygen index >40, PaCO₂ >12KPa for at least 3 hr, post ductal PaO₂ < 40 mmHg for more than 2 hr, PaCO₂ >12KPa for at least 3 hr, AaDO₂ >610 mmHg for more than 8 hr and FiO₂ >0.9 for more than 24 hr. These criteria can vary between ECMO centres. Unfortunately there is a lack of conclusive

evidence-based data regarding the impact of ECMO on mortality and morbidity in patients with severe CDH^{1-4, 35-41}. Some centres have shown decreased or unchanged survival rates whilst many others have shown ECMO to have improved outcomes over the ten to fifteen years. In 1996, The UK Collaborative ECMO Trial Group published a randomised controlled study of all neonates receiving ECMO including those with CDH¹. They found that those CDH patients treated with ECMO had a mortality rate of 78% and survivors had a significantly increased morbidity with only 6% being neuro-developmentally 'normal'. In contrast researchers such as, Heiss⁴, West³⁸ and Bartlett³⁷ have presented increased survival rates for those neonates with CDH who received ECMO.

With the lack of high power evidence-based research to categorically decide on the usefulness of ECMO for CDH cases, it is a difficult decision when thinking about the possibility of referral. If one is considering a referral to an ECMO centre, the general advice would be to contact a centre early, when the neonate is evidently failing on conventional management.

Surgical treatment

The timing of surgical repair has changed from immediate repair to stabilisation and delayed repair^{43, 44}. Controversy surrounds the surgical timing of repair as again there is a lack of large, multi-centre randomised control trials to give a definitive answer. Two small randomised control trials comparing early (<24hr) versus late (>24 hr) repair of CDH exist^{45, 46}. Neither showed any significant difference in mortality between the groups. The Cochrane Systematic Review in 1996 also concluded there was no clear evidence favouring delayed or immediate repair⁴⁷. Repair can occur successfully whilst on ECMO at specialist centres⁴⁸.

Despite the controversy, many neonatal units would advocate delayed correction as it gives time to achieve cardiorespiratory stability, to look for other anomalies and to discuss the therapeutic options with the parents⁴⁹.

Currently the accepted surgical technique is to use a subcostal incision and if a hernial sac is present it should be excised (**FIGURE 3**). The abdominal viscera are examined and the hernia is reduced by gentle traction. The defect is then closed and if it is large a prosthetic patch may be

required^{50,51}. The use of chest drains is again controversial, as is the use of suction. Research suggests that if suction is used it should be limited to 5 cmH₂O⁵¹. New advances in surgical management are evolving and include thoracoscopic techniques.

Postoperative care

The aim is to maintain the cardiorespiratory stability achieved preoperatively, with an incremental weaning from intensive care support. Many CDH cases experience a slow wean from ventilation, during which time the focus on nutritional support and close monitoring for complications is paramount.

Survival

It is doubtful that the true survival figures will ever be known, as CDH can be lethal in the antenatal as well as postnatal period. Many neonates with CDH die before the opportunity for the various degrees of neonatal care available worldwide are put into place. The international CDH Study Group database with over 1600 patients reports an overall survival of 66%, but this may not include all deaths due to CDH. Various centres, including the authors' own, report survival figures of 85-90%. The ECMO versus non-ECMO debate continues. Without a true severity predictor it is difficult to assess either. In addition bias can occur at many levels. Centres with the highest results are often accused of selecting the neonates who are more likely to survive anyway by virtue of neonates dying before they arrive at the centres.

Morbidity and follow-up

With potentially increased numbers of survivors there will be an associated increase in morbidity, related to iatrogenic lung injury and postoperative and ECMO complications. Survivors also have significant, initially hidden, morbidity. A number of institutions, not least those in Rotterdam and Boston, have set up large multidisciplinary teams to care for these infants and their families. Team members include physiotherapists, developmental psychologists, genetic counsellors, a coordinating physician and an array of organ specific specialists.

Reports suggest up to 45% of survivors have neurological deficits. Many are below

the 5th growth centile requiring significant nutritional input. The gastro-oesophageal reflux rate is reported as between 16-62% in the literature^{19,30-33}. Hearing loss and orthopaedic problems, including scoliosis and chest asymmetry are not uncommon. There has been much debate regarding lung growth and pulmonary outcome. Pulmonary function tests indicate up to 25% of infants may develop a chronic obstructive airways picture. In addition VQ scanning into early childhood suggests a possible limitation of vascular development of the affected lung, emphasising that lung growth needs to be determined in terms of both the respiratory tree and the vasculature.

The future

The past has taught us that CDH neonates do not die from lung hypoplasia alone. Driving neonates to a postductal PaO₂ >100mmHg to become a 'survivor' with high pressure ventilation and inotropes does not improve outcome. Iatrogenic barotrauma does kill neonates with CDH. It has become apparent that pulmonary hypertension and right heart failure are the real contributors to lethality and that the end of the 'honeymoon period' may be a cardiac event, with modulation of nitric oxide the key. The near future may be based on so-called gentle ventilation and focusing more on the pulmonary and systemic cardiovascular systems.

Further into the future we may be able to make lungs grow. In 1998 Nobuhara et al demonstrated perfluorocarbon-induced lung growth in terms of increased lung volume and alveolar numbers with partial liquid ventilation⁵³. Fauza et al in 2001 demonstrated a two-fold increase in lung volume with seven days of perfluorocarbon liquid distension with CPAP whilst on ECMO⁵⁴. A subsequent pilot study suggested benefit and a definitive trial is being constructed. In 2003 Walker et al presented six cases with up to 50% increase in contralateral volume and 300% ipsilateral volume, with all cases surviving⁵⁵. There are a number of important issues with such approaches before they can be accepted as the future of severe CDH management, as some purport. These include whether an increase in lung volume is an actual lung growth of healthy alveoli and if such a 'growth' can be achieved in the limited time that the neonate is on ECMO. The future may bring the ability to conventionally ventilate

very small immature lungs safely⁵⁶ and by supporting the cardiovascular system postnatal growth of lungs can occur.

What is certain from the worldwide work on CDH that has been done in the past, is that without appropriate multi-centre randomised control trials, there will be more bias and less knowledge.

Conclusions

The mortality and morbidity of CDH remains high despite recent advances in treatments. A structured approach with well written guidelines, based on the best available clinical evidence, along with appropriate training, is vitally important if the mortality and morbidity of the disease are to improve. In many cases the initial resuscitation and stabilisation in the first 24 hours is key to an optimal outcome. The lack of high powered evidence regarding the use of various techniques highlights the desperate need for randomised controlled multi-centred trials. A worldwide concerted effort to develop an evidence base and gain definitive answers, will go some way to reducing mortality in the coming years.

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