

RECENT ADVANCES

Recent advances in congenital diaphragmatic hernia

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Congenital diaphragmatic hernia (CDH) is a common birth defect which continues to challenge paediatric surgeons and intensivists. Affecting approximately 1:2500 births, a baby with CDH is born every 24–36 hours in the UK.¹

respiratory pathology. This trial showed no benefit for HFOV compared to conventional ventilation.⁸ Reports from single institutions continue to extol the benefits of HFOV in newborns with CDH, in particular when this is used as an elective ventilatory strategy.^{9,10} A large multi-centre trial is needed to address this question.

For the majority of newborns in whom CDH is an isolated anomaly, the degree of associated pulmonary hypoplasia remains the major determinant of survival. Recent “single institution” reports have shown encouraging results, with survival figures exceeding 80%.^{2–4} However, these should be recognised as reports on live-borns arriving at a specialist centre. There is no doubt that a significant proportion of cases continue to succumb either antenatally or in the first few hours of life.⁵ Interestingly the earliest reports of surgery for CDH showed survival figures similar to the recent successful outcomes from specialist centres.⁶ This was a reflection of natural patient selection; neonates operated on in early series were those who had survived the first crucial minutes and hours—that is, those least affected by pulmonary hypoplasia and hypertension. Improved resuscitation and neonatal critical care has resulted in a very different patient population reaching surgery. It has taken more than 50 years to regain these impressive survival figures with more challenging patients.

ECMO as therapy for newborns with respiratory failure became widely available during the 1980s. Its potential benefits were tested in the UK by a collaborative prospective randomised trial. The trial failed to show improved outcomes for CDH, however entry criteria have been criticised as being severely stringent—necessitating “near unsalvageable” respiratory failure before recruitment.¹¹ A subsequent Cochrane review on the use of ECMO in neonates identified four randomised trials, of which two included infants with CDH. This review commented that survival benefit is seen for all newborns—but is least evident in CDH. Longer term follow up data are needed to assess ongoing morbidity and mortality in this severely affected group of patients.¹² The UK ECMO group have recently highlighted these issues, showing that at 67 months median follow up only 7/73 children (10%) are free of significant neurodevelopmental delay, and medical and surgical intervention.¹³ Long term follow up is warranted for all patients with CDH, not merely those who have been treated with ECMO. Close attention to CDH survivors reveals a high incidence of long term morbidity, particularly focused on the respiratory and gastrointestinal systems.^{14,15} Specialist multi-disciplinary clinics are evolving in many centres, including Liverpool, to provide dedicated care for the needs of these vulnerable patients.

CURRENT TREATMENT STRATEGIES: EVIDENCE BASE

Advances in neonatal intensive care and ventilation have greatly improved the outlook for live-born infants with CDH. The introduction of ventilatory adjuncts such as high frequency oscillatory ventilation, inhaled nitric oxide, and extracorporeal membrane oxygenation (ECMO) are supported by several anecdotal reports. However, these interventions have not shown true survival benefits for CDH in randomised trials. Inhaled nitric oxide has been the subject of a Cochrane review in term or near term infants with respiratory failure. This report concluded that the use of nitric oxide could be supported in general for infants with pulmonary hypertension and respiratory failure. However, benefit was not seen for patients with CDH; the review further noted that some reports have indicated a worse outcome in this group.⁷ A large randomised trial focused solely on CDH may resolve this issue.

High frequency oscillatory ventilation (HFOV) has been analysed by the Cochrane group for its efficacy as a “rescue” therapy for babies in whom conventional ventilatory strategies fail. The report found only one randomised trial which included infants with a wide variety of

Barotrauma has now been recognised as a significant cause of mortality and morbidity in CDH.¹⁶ The concept of “gentle” ventilation/permissive hypercapnia was proposed by Wung and colleagues at Columbia University, New York in the 1980s.¹⁷ The protocol is designed to minimise barotrauma by strictly limiting the peak inflation pressure. Ventilation is aimed at keeping pre-ductal oxygen saturations above 85%, while tolerating rises in PaCO₂. Survival figures >80% have been reported from New York and Boston.^{4,18} This represents one of the biggest single advances in CDH care in recent years and has led to declining use of ECMO.

Delayed surgical repair of CDH following a period of preoperative stabilisation is generally employed in most centres. Few paediatric surgeons support emergent repair.¹⁹ This approach

Abbreviations: CDH, congenital diaphragmatic hernia; ECMO, extracorporeal membrane oxygenation; HFOV, high frequency oscillatory ventilation

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permits full assessment and stabilisation of labile physiology. Increasingly cardiologists can play a pivotal role in serial echocardiographic assessment to monitor ductal shunting and pulmonary hypertension. A team approach is crucial to guide the optimum timing of surgery, a strategy currently employed at our institution and other specialist centres. Operation via a subcostal incision gives access to the diaphragm where primary repair following visceral reduction or a prosthetic implant may be needed to close the defect. There is however a high rate of patch disruption/herniation with artificial prostheses as the patients grow.²⁰ Recent interest has therefore focused on the use of bio-prostheses²¹ in an effort to provide a “scaffold” that grows with the patient. Laparoscopy has been utilised in selected cases to repair CDH. Caution should be exercised in high risk newborns.²²

HIDDEN MORTALITY AND “TRUE” OUTCOMES

One should be sceptical when interpreting studies on CDH that report excellent survival. Such reports may include selection bias and fail to recognise “hidden mortality”²³ as has been shown by recent communications from both Newcastle, UK and Ontario, Canada.⁵ ²⁴ A controversial area which has been highlighted is the difference in survival between infants treated in “high volume” and “low volume” centres. In two studies published this year, “high volume” centres (treating more than five or six cases per year) performed significantly better.²⁵ ²⁶ Is there a case for CDH management being designated to specialist centres in the UK?

FETAL THERAPIES: WHERE ARE WE NOW?

For over two decades pioneering efforts have been deployed to rescue lung growth in the severely affected fetus with CDH. The work of Harrison’s group in San Francisco initially focused on open antenatal repair of the diaphragmatic defect.²⁷ Outcomes were hampered by technical surgical difficulties, problems maintaining tocolysis, and a high rate of preterm delivery. Further advances resulted from the key observation that babies born with congenital laryngeal atresia (preventing the normal efflux of intraluminal lung liquid) develop tremendous pulmonary growth.²⁸ This finding prompted the concept that occluding the fetal trachea (the “PLUG” (plug the lung until it grows) procedure) in pulmonary hypoplasia associated with CDH could increase lung growth and improve outcomes. Initial attempts at open tracheal occlusion were succeeded by a modified endoscopic technique—so-called FETENDO (FETal ENDoscopic) surgery.²⁹ A National Institute of Health sponsored randomised trial led by the San Francisco group disappointingly showed no survival benefits compared to elective delivery at specialist centres with optimal postnatal CDH care. The trial was terminated early by the steering committee due to unexpectedly good outcomes in the control group.³⁰ In Europe fetal tracheal occlusion (FETO) continues to be explored—further technical refinement may uncover survival benefits in high risk patients.³¹

The issue of determining accurate antenatal prognostic markers has proven problematic throughout these ground breaking studies. The ability to detect those fetuses most severely affected in the prenatal period would be invaluable in selecting those for high risk interventions. Despite a wide variety of indices being suggested, there is as yet no robust marker to determine accurate prognosis. Attention has focused on the lung:head ratio (LHR); calculating the ratio between cross-sectional lung area (contralateral to the defect) and head circumference. The original description of the technique from Harrison’s group found that an LHR <0.6 was universally fatal; in subsequent studies this has been

modified to <1.0. Larger prospective studies are required to validate these observations.³² ³³ It is vital that paediatric surgeons are involved with obstetricians and neonatologists in the counselling process for all prenatally diagnosed CDH cases. Outcomes are steadily improving in those centres with a specialist interest in this birth defect.⁴ ³⁴

BASIC SCIENCE: TRANSLATIONAL RESEARCH

Improved understanding of normal and abnormal lung development may lead to new therapeutic targets for lung hypoplasia and the associated lethal pulmonary hypertension. Progress in developmental biology has uncovered a host of genetic and growth factor/cell signalling pathways involved in early branching morphogenesis, many of which are disturbed in experimental models of CDH and pulmonary hypoplasia.¹ ^{35–37} A number of syndromes are identified in CDH (for example, Fryn’s syndrome); these are often accompanied by other extensive and life threatening defects.³⁸ ³⁹ No specific causal gene(s) defects have been identified in humans; screening studies are underway to identify likely candidates (PK Donahoe and JJ Schnitzer, personal communication).

The importance of mechanical factors in regulating lung development has been shown through work on the tracheal PLUG, the role of lung liquid and studies on fetal breathing movements.⁴⁰ ⁴¹ Further advances may arise from improved understanding of primitive events regulating airway physiology—lung growth.⁴² The mechanisms underlying abnormal pulmonary vascular development are undergoing significant scrutiny.⁴³ Basic science studies have also illustrated the potential benefits of antenatal corticosteroid therapy in experimental CDH.⁴⁴ As improved outcomes are steadily unfolding, a clinical trial is warranted to test this therapy in the most severely affected fetus with CDH. Selecting these patients remains a challenge for ongoing studies. The goal for quality research in CDH is to translate experimental observations into clinically safe and effective therapies. Such efforts will be significantly aided by ongoing collaboration between dedicated researchers with the international CDH Study Group⁴⁵ and the interplay with active parent support groups such as CHERUBS.

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