Evidence-Based Management of Infants with Congenital Diaphragmatic Hernia

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The mortality rate associated with congenital diaphragmatic hernia (CDH) varies widely between centers and remains relatively high despite widespread use of new therapeutic modalities. Many of these have been implemented without properly controlled studies. Over the past 10 to 15 years, only 9 randomized trials enrolling a total of approximately 250 infants with CDH have been published. The limited evidence available suggests that better outcomes are observed by delivering infants with CDH at experienced centers, by delaying surgical repair until hemodynamic and respiratory stability is achieved, and by the judicious utilization of nonaggressive mechanical ventilation and permissive hypercapnea. Other therapeutic modalities, such as high frequency oscillatory ventilation, inhaled nitric oxide, and ECMO, may provide additional advantages for selected infants. There is a dire need to establish networks of centers that manage enough infants with CDH, to conduct appropriately sized randomized trials that can answer some of the critical questions about the management and long-term outcome of these infants.

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The mortality rate associated with congenital diaphragmatic hernia (CDH) varies widely between centers and remains relatively high despite widespread implementation of new therapeutic modalities. Experienced referral centers with extracorporeal membrane oxygenation (ECMO) describe that a large proportion of infants with CDH can be saved.¹ In contrast, reports focusing on infants with CDH diagnosed antenatally or regional experiences that are likely to include most cases of CDH in a defined geographic area have not consistently shown a lower risk of mortality.²,³ This “hidden mortality” of CDH can be explained in part by the occurrence of intrauterine deaths (spontaneous or pregnancy terminations) as well as that of severely affected infants who die before transfer to a center capable of their management. In a recent article, Stege and coworkers implied that the actual mortality of CDH has not been affected by new therapies when complete case ascertainment is achieved.⁴ They argued that pregnancy terminations and postnatal deaths occurring before transfer to referral centers are ignored in most intervention studies, thereby falsely inflating the positive effects of the treatment.

Independent of whether overall mortality for infants with CDH has decreased or not, it is clear that many new therapeutic modalities used in infants with this problem have been implemented without properly controlled studies. In view of the low relative frequency with which CDH occurs, it is not surprising that there are very few randomized trials involving fetuses/infants with this condition. In fact, our literature search while preparing this review only revealed 9 randomized trials conducted over the past 10 to 15 years, enrolling only a total of approximately 250 infants with CDH.

This chapter will attempt to evaluate the level of evidence to justify certain aspects of the clinical management of infants with CDH. This is of particular importance since it has been noted that more than 97% of the clinical research in pediatric surgery consists of retrospective data.⁵ The literature on management of CDH is no different than the rest of the surgical literature, and there is a paucity of controlled trials. We will try to categorize the levels of available evidence (Table 1) as described by Wiswell,⁶ and accept the notion that interventions used in the management of infants with CDH with a potentially very low risk of significant side effects, i.e., placement of a nasogastric tube for decompression of the stomach, may be recommended mainly on the basis of experience or pathophysiologic plausibility. More specifically, we will re-

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view the evidence regarding the role of antenatal corticosteroids in the management of fetuses with CDH, the timing of surgical correction of CDH, and the use of postnatal interventions, such as surfactant administration, various ventilatory modalities, and the preliminary evidence about the use of perfluorocarbon-induced lung growth. Other chapters in this issue address therapeutic interventions such as administration of inhaled nitric oxide and ECMO.

The International CDH Registry

To study adequately complex and uncommon medical problems, it is often necessary to gather the experience of many centers, with the hope that the information collected can serve as the basis for a better definition of the problem, and potentially for planning multicenter trials capable of answering crucial questions about therapeutic interventions. One of the most significant steps forward aimed at addressing the problem of CDH was the establishment of an International Registry for infants with this disease. The CDH study group was formed in 1995 to collect data from multiple institutions in North America, Europe, Japan and Australia. Participating centers completed a registry form on all live-born infants with CDH, which contained demographic information and data about surgical management and outcome. The initial report included 62 centers, with 461 patients entered.7 Delayed surgical repair was found to be the favored approach at that time, and overall survival was around 60%. The database also permitted reporting on rare disorders that feature CDH, such as Fryns syndrome, and allowed investigators to devise risk assessment tools for CDH that may predict outcome across institutions.8,9 More recent contributions have involved much larger numbers of infants with CDH and have commented on a variety of aspects of the management of these infants.10,11 While this information is quite useful, it is important to recognize that it reflects observational data and hence does not represent the same level of evidence as controlled trials. Ultimately, the hope of establishing this registry was that stratifying neonates with CDH into broad risk groups would allow better comparisons of outcome data from different centers, and that this working group could serve as the platform to launch multicenter intervention trials.

Antenatal Corticosteroids in the Management of CDH

Abnormalities of fetal lung development and maturation have been reported in animal models of CDH and human fetuses with this entity.12-15 These are reviewed in detail by Tibboel and Rottier elsewhere in this issue. Furthermore, exposure to antenatal corticosteroids has been shown to result in improvement of lung maturation in animal models of CDH.16-19

Currently, administration of antenatal corticosteroids is recommended on all pregnancies between 24 and 34 weeks’ gestation if delivery is expected before 34 weeks and there are no contraindications to their use.20 While this recommendation does not specifically address pregnancies in which the fetus is known to have a CDH, in the setting of preterm labor before 34 weeks, antenatal corticosteroids should be offered as in otherwise uncomplicated pregnancies. To date there are no controlled trials of antenatal use of any corticosteroid in a population of pregnant women known to have a fetus with CDH. Indeed, the only clinical report on this area is a series of three patients who received multiple doses of betamethasone starting between 24 and 26 weeks and continued bi-weekly until term.21 However, whether antenatal corticosteroids should be provided beyond 34 weeks of gestation in pregnancies complicated with CDH in an attempt to “mature” the fetal lung remains uncertain and cannot be recommended at this time. Moreover, in view of the lack of benefit of repeated courses of antenatal corticosteroids in pregnancies at risk for preterm delivery and the potential for side effects with repeated exposure to them, administration of more than one course of these hormones to women known to carry a fetus with CDH is also not recommended.22 Despite this evidence, data from the International CDH Registry demonstrates that at least 14% of infants over 34 weeks’ gestation with a prenatally diagnosed CDH received corticosteroids.

Whereas there may be potential advantages of planning
the timing of delivery of a fetus known to have a CDH, there
are no controlled trials to support either scheduling these
deliveries electively or opting for a cesarean section versus
the vaginal route.23,24 This notwithstanding, given that the post-
natal management of these infants often involves utilization
of invasive therapies, such as inhaled nitric oxide, high fre-
quency ventilation, and ECMO, whenever possible, delivery
of these infants should occur in a center experienced in the
use of these modalities. Further support for this recommen-
dation stems from reports of increased survival for infants
with CDH managed in “high-volume” centers.1,25
After delivery, endotracheal intubation is usually required
while avoiding bag-and-mask ventilation, which may distend
the stomach and intestines with air and may compromise
further pulmonary function. Placement of a nasogastric tube
for low intermittent decompression of the bowel is recom-
mended. Gas exchange and acid-base status should be as-
essed preferably via an arterial catheter.

Timing of Surgical Correction
The timing of surgical repair has gradually shifted from emer-
gent repair to a policy of stabilization using a variety of ven-
tilatory strategies before operation.1,7 However, it remains
controversial whether delayed surgery is actually beneficial.
Two small randomized trials (total of 86 infants enrolled)
comparing early (<24 hours) versus late (>24 hours) sur-
cational repair of CDH among infants who were symptomatic
at or shortly after birth have been published.26,27 Neither
showed any significant difference between groups in mortal-
ity, the primary outcome. These data were incorporated into
a recent Cochrane Systematic Review on the effects of late
defined as more than 24 hours of age) versus early (defined
as within the first 24 hours after birth) surgical correction
of CDH on survival to hospital discharge.28 The authors of this
review concluded that there is no clear evidence favoring
delayed (when stabilized) as compared with immediate
(within 24 hours of birth) surgical repair of CDH, but a
substantial advantage to either one could not be ruled out.
They recommended conducting a large, multicenter random-
ized trial to help answer definitively this question. Nonethe-
less, given the position of equipoise derived from these data
and the fact that often it is important to have time to look for
other anomalies, to discuss potential therapeutic alternatives
with the parents, and to engage the opinion of other consult-
ants, our current recommendation is to adopt a conservative
approach and delay surgical repair of the CDH until the in-
fant has had an opportunity to stabilize from a hemodynamic
and respiratory point of view.29

Use of Surfactant
Many studies using different animal models of CDH have
demonstrated that their lungs are surfactant deficient and
that, in the lamb model of CDH, the prophylactic adminis-
tration of surfactant is more effective than delayed use.12-14,30
There are also data to suggest that the lungs of human infants
with CDH have a relative deficiency of some components of
surfactant and that their surfactant pool size may be altered.15,31
These are reviewed in more detail in chapter 4 of this
issue.

Several small case series have described the use of exoge-
nous surfactant in infants with CDH. The original report by
Bos and coworkers described the administration of an ani-
mal-derived surfactant in 5 sick neonates, 4 of whom had a
CDH, while the remaining infant had a cystic adenomatoid
malformation.32 There was only a transient improvement in
oxygenation in half of the infants. Clinical benefit was also
described in a subsequent small series of infants with CDH
survived with surfactant, which included some preterm neo-
nes.33 In a more recent review by Bohn and coworkers,
these authors acknowledged that their experience with the
use of rescue administration of bovine surfactant was less
impressive, with little or no improvement in gas exchange,
although no specific descriptions of patients or statistics
were provided.34 In addition, these authors commented that “a
clinical trial of surfactant, given prophylactically before the
first breath in infants with a prenatal diagnosis of CDH, was
in progress.” Unfortunately, to date there are no published
randomized, controlled trials of the use of surfactant among
infants with CDH. However, the use of a bovine-derived
surfactant (beractant) was evaluated in a small, randomized
trial of 17 infants >34 weeks’ gestation with CDH already on
ECMO.35 Even though there was evidence of decreased con-
centrations of surfactant protein A in the tracheal aspirates of
these infants, a surrogate marker for surfactant deficiency, no
clinical benefit was observed in lung compliance, time to
extubation, or duration of oxygen therapy with administra-
tion of several doses of beractant. Notwithstanding, this very
preliminary and anecdotal information as well as the animal
studies mentioned before seem to have been interpreted as
important data to support the use of surfactant in the man-
gement of infants with CDH.

Judged by descriptions in the literature published during
the last decade and data from the International CDH Registry,
the use of surfactant has been incorporated alone or as part of
a more comprehensive strategy into treatment protocols for
patients with CDH at many centers worldwide.36-40 Observa-
tional data from this Registry do not suggest any benefit
with the use of surfactant in preterm or term infants with
CDH, or in those receiving surfactant while on ECMO.31,39,40
Also, some of the experiences described in the literature sug-
gest that very few infants exhibit a clinical response to sur-
cactant administration.34,37 Therefore, based on the lack of
definitive evidence and the availability of only limited obser-
vational studies and biologic plausibility, administration of
surfactant to infants with CDH cannot be recommended,
with the exception of participation in well-designed clinical
trials, or in the setting of significant prematurity when, be-
sides CDH, the infant may also exhibit respiratory distress
due to true surfactant deficiency.

Ventilatory Strategy
Most infants with CDH who become symptomatic in the first
couple of hours after birth will require endotracheal intubation and
mechanical ventilation. If it is known antenatally that the infant has a CDH, the use of bag and mask ventilation in the delivery room should be avoided as distention of the stomach and intestines with air further compromises pulmonary function. This may be harder to avoid if the diagnosis has not been made before birth.

One of the main goals of mechanical ventilation on any patient is to sustain adequate gas exchange, but what is adequate for an infant with CDH has not been well characterized. Our limited understanding of the significance of the degree of lung hypoplasia and the role of pulmonary hypertension in the pathophysiology of CDH led to excessive use of ventilatory pressures and oxygen in the management of these infants. Boix-Ochoa first reported that there were differences in pH and PaCO₂ between survivors and nonsurvivors with CDH. Additional data published by Drummond and others demonstrated the relationship between pH, PaCO₂ and pulmonary vascular resistance, and also reversal of ductal shunting by increasing pH and decreasing PaCO₂. Translation of these data into clinical practice probably contributed to the wide use of hyperventilation, often with high ventilatory pressures and fast rates, as the primary ventilator strategy for CDH. Subsequently, Wung and collaborators suggested that much of the mortality in CDH infants was in fact due to ventilator-induced lung injury and advocated for a less aggressive approach allowing for higher PaCO₂ values. Clinico-pathological studies have confirmed this correlation.

The current ventilatory strategy used in most centers has followed this trend and focuses on minimizing barotrauma by allowing spontaneous ventilation with minimal set respiratory rates, limiting ventilatory pressures usually to less than 25 cm H₂O, tolerance of high PaCO₂, minimal sedation, and avoidance of paralysis. Using this strategy, several groups have achieved relatively high survival rates. Also, a suggestion that using lower levels of positive end expiratory pressure may be advantageous after surgical repair has been made.

The utility of high frequency oscillatory ventilation (HFOV) in patients with CDH has been a subject of debate. Paranka and colleagues showed that HFOV was of little benefit when used in a high-pressure lung recruitment strategy in patients with CDH. Others have suggested that, when used as the initial mode of therapy, HFOV may be a more effective mode of ventilatory support than conventional ventilation in CDH. However, interpretation of these observational data is difficult since the effect of HFOV often cannot be separated from that of other cointerventions or approaches, and there are also reports demonstrating no benefit of this approach.

The optimal mode of ventilation for patients with CDH is not clear. However, regardless of the ventilatory approach used, management strategies designed to limit lung distention and inspiratory pressures while allowing some degree of permissive hypercapnea are recommended, since they seem to be associated with a higher likelihood of survival. Nonetheless, as is the case with most therapeutic options in CDH, these recommendations are based on observational studies and have not, to date, been validated with controlled studies. Moreover, the potential long-term effects of allowing hours or days of relatively low pH, high PaCO₂, and often borderline oxygenation (ie, accepting borderline saturations percutaneously) have not been determined. Conducting such studies is particularly important given the high likelihood of neurodevelopmental abnormalities observed among survivors. More specific information on long-term follow up of infants with CDH can be found in the chapter by West and Wilson of this issue.

**Perfluorocarbon-Induced Lung Growth**

The use of perfluorocarbons as a means to oxygenate and ventilate a diseased lung has been studied extensively in animal models of lung injury. However, the clinical evidence examining its potential role in neonatal diseases remains scarce. Studies conducted in the lamb model of CDH have demonstrated that instilling perfluorocarbons into the lungs (partial liquid ventilation) while providing mechanical ventilation was able to induce progressive lung growth over several days. Preliminary supportive observations in infants with CDH treated with this approach have also been reported. Recently, a multicenter, prospective, randomized pilot study of this intervention in 13 infants with CDH was reported. All infants enrolled, 8 in the perfluorocarbon group and 5 in the conventional mechanical ventilation group, were near term (average of 37 weeks) and had been placed on ECMO at the time of treatment assignment. Whereas no significant improvements were demonstrated in duration of ECMO (9.8 ± 2.3 days versus 14.5 ± 3.5 days, P = 0.58, respectively) and survival (75% versus 40%, P = 0.50, respectively), this preliminary experience demonstrated the feasibility of using this technique and may open the door for future, more definitive trials of this intervention. An important caveat to be considered relates to the fact that all infants studied were on ECMO at the time of the intervention. Therefore, the potential usefulness of this technique for infants not on ECMO remains essentially unknown.

**Summary**

Although the management of infants with CDH remains a major challenge in perinatology and neonatology worldwide, most current therapeutic recommendations are based primarily on observational studies, historical data, and biologic plausibility derived from animal studies. There is a paucity of large randomized, controlled studies among infants with this condition. Whereas in the absence of such trials it is impossible to make sound therapeutic recommendations, current evidence suggests that better outcomes might be achieved by delivering infants with CDH at experienced centers, by delaying surgical repair until an acceptable degree of hemodynamic and respiratory stability is established, and by judicious utilization of nonaggressive mechanical ventilation and permissive hypercapnea. Other therapeutic modalities, such as high frequency oscillatory ventilation, inhaled nitric
oxides, and ECMO, may provide additional advantages for selected infants. Only by establishing networks of centers in which enough infants with CDH are managed will we be able to conduct appropriately sized randomized trials that can contribute to answer some of the crucial dilemmas about the management of these infants and can shed light on their long-term outcome.

References


