Many infants with CDH can be managed with conventional mechanical ventilation and pharmacotherapy. However, some infants will require levels of ventilator support that are not compatible with survival. In these circumstances, extracorporeal membrane oxygenation (ECMO) has been used with varying results. The indication, type, and timing of ECMO in relation to surgery continue to evolve in an attempt to improve the outcome. At the same time, there is growing body of literature showing adverse outcomes among infants with CDH treated with ECMO, raising questions about the usefulness of ECMO in CDH. This paper reviews some of the controversies associated with the use of ECMO in CDH.

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The Role of Extracorporeal Membrane Oxygenation in the Management of Infants with Congenital Diaphragmatic Hernia

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Role of ECMO in Hypoxemic Respiratory Failure

Extracorporeal membrane oxygenation is a form of long-term cardiopulmonary bypass for the treatment of patients with severe but potentially reversible hypoxemic respiratory failure (HRF). ECMO is used to support lung and/or heart function by means of extracorporeal artificial organs. Even though a small number of prospective randomized trials showed improved mortality and morbidity with the use of ECMO in severe HRF, it was not until 1996 when the UK Collaborative ECMO Trial Group published their findings that ECMO became a standard modality for treatment of infants with HRF.1

CDH and ECMO

The first report of ECMO use for infants with CDH was by German and coworkers in 1977.2 He reported on four infants with severe respiratory failure who were placed on ECMO after repair with one survivor. ECMO was initially used to treat infants that developed severe hypoxemia after surgical repair of CDH. CDH was treated as an emergent surgical condition in the 1980s; hence, the infants who were placed on ECMO were all placed on after repair. In the late 1980s, with growing understanding of the role of pulmonary hypertension in CDH, surgical correction in many centers became a planned rather than an emergent procedure.3,4 Preoperative stabilization with delayed repair became standard practice. ECMO has been increasingly used as a component of a strategy of preoperative stabilization, and the large majority of infants with CDH who receive ECMO are placed on bypass before surgical correction.

Criteria to Use ECMO

ECMO is generally reserved for infants that fail maximal medical management. Over the last several years, the role of ventilator-induced lung injury in CDH has been increasingly appreciated. Studies have suggested that the gentle ventilation and permissive hypercapnea lead to improved outcome.5 Because of these findings, some centers now institute ECMO in infants with CDH earlier than in the past to avoid ventilator-induced lung injury. However, this approach has not been systematically studied. The criteria used to deter-
mine failure of conventional therapy has changed markedly over the past 20 years. A number of different parameters have been used, all in an attempt to predict those patients with a high risk of death (Table 1). The UK ECMO trial used an oxygenation index (MAP × FiO2/postductal O2 × 100) for all patients, including those with CDH, but these criteria may be too restrictive for infants with pulmonary hypoplasia. Given the number of indications, there is also a marked variation in practice between institutions. This makes interpretation of outcomes very difficult. Currently, the most widely used indication for ECMO is, “failure to respond to medical therapy.” Clearly, this may vary depending on the center and patient, but strict entry criteria that can accurately predict mortality for ECMO in patients with CDH have not been published. Given the uncommon nature of the disease, it is highly unlikely that there will be a large published series validating a certain entry criteria.

**Timing of ECMO**

As mentioned above, ECMO was initially used after repair of the diaphragm defect, but this has changed. To better understand the impact of use of ECMO for preoperative stabilization in infants with CDH, the Congenital Diaphragmatic Hernia Study Group reported on this question. The CDH Study Group is a voluntary collection of centers caring for liveborn infants with CDH. Starting in 1995, data such as patient demographics, management, and outcome were collected from participating centers. By 2002, data for 2077 patients with CDH had been added to the registry, of which 770 patients (37%) were treated with ECMO. Analysis of the timing of ECMO showed that only 15% of the infants were placed on ECMO after CDH repair. Furthermore, according to the registry data, there has been a progressive reduction in the number of infants treated with ECMO after repair. In 1995, ECMO was used after repair in 20% of the patients as opposed to only 5% in 2001. These data clearly show how ECMO has evolved to be a component of preoperative stabilization as opposed to a postoperative rescue therapy.

**Efficacy of ECMO**

ECMO provides effective but short-term support for respiratory failure, and therefore, reversibility of the underlying disorder is important when considering patients for ECMO. Infants with HRF because of meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), and sepsis are good candidates for ECMO therapy because of the reversible, time-limited nature of these disorders. The reported survival rate for infants undergoing ECMO for MAS, RDS, and sepsis is 94%, 84%, and 75%, respectively. In contrast, the use of ECMO in CDH presents an interesting dilemma. Infants with CDH can have severe HRF because of pulmonary hypertension and pulmonary hypoplasia. Pulmonary hypertension is potentially reversible, but the severity of pulmonary hypoplasia is variable and possibly irreversible. In some infants, the pulmonary hypertension may be persistent as well, and this can lead to progressive right heart failure. These underlying problems may lead to poor outcome for infants treated with ECMO. This would appear to be the case as the overall survival of infants with CDH reported to international ECMO registry is about 52% and is the lowest among all etiologies of neonatal HRF requiring ECMO. The UK Collaborative Trial, which proved the utility of ECMO in HRF, failed to show a significant improvement in outcome for ECMO in infants with CDH with a survival rate of less than 20%. Furthermore, analysis of ECMO registry data for neonates requiring ECMO for CDH by Stevens and coworkers shows that the survival rate between 1990 and 2001 has decreased from 64% to 52%. There are, however, other studies that have shown an improvement in mortality with the use of ECMO. The unclear benefit of ECMO in CDH was made murkier by two studies which showed a similar survival rate, but one used ECMO in 50% of the infants with CDH whereas the other in only 1%, suggesting that interventions other than ECMO may be responsible for improved outcome.

Based on previously described observations, better patient selection criteria may improve morbidity and mortality among infants with CDH that require ECMO. Among the various factors that may have a role in determining the outcome of CDH, pulmonary hypoplasia is thought to be the most important. However, the degree of pulmonary hypoplasia is difficult to assess in CDH. There are no good predictors radiographically. Attempts have been made to use alveolar arterial oxygen gradients, arterial oxygenation, best preductal hemoglobin saturations, preductal arterial oxygen tensions, and the severity of hypercarbia during the stabilization period. Based on different combinations of the above-mentioned parameters, some centers have developed algorithms for stratifying infants based on the degree of pulmonary hypoplasia and offer ECMO only to infants who have the best chance of survival (Table 2). However, medical stabilization
strategies differ between centers, and as a result, ECMO exclusion criteria are not standardized and vary from center to center. Furthermore, the spectrum of disease severity is so wide that this leads to controversy when comparing outcomes of centers based on exclusion criteria for ECMO in CDH. The CDH Study Group has been working since 1995 on developing treatment-independent risk assessment tools to accurately compare outcome among centers according to the severity of the disease. They looked at several factors that are available to the clinician in the first 5 minutes, such as gender, race, birth weight, Apgar scores, immediate distress, CPR, estimated gestational age (EGA), side of hernia, and prenatal diagnosis. Of these, birth weight and Apgar scores were found to be most predictive of outcome, and based on these, the group published a logistic regression equation that estimates the severity of CDH. Applying this equation, the group showed a 74% survival in the low risk group as opposed to 16% in the high risk group. This could be a tool to identify a CDH patient that is likely to have the best possible outcome on ECMO. However, when Wilson and coworkers analyzed their center’s outcomes, they found that the predicted outcome was lower than the actual outcome. They concluded that the equation is useful for comparing outcomes between centers, but not predicting individual patient outcome. Keshen and coworkers analyzed CDH registry data using the above equation and could only show benefit for ECMO in the very high risk patients. Given the variables of patient type, patient selection, criteria for use, and center variability in management, it is difficult to conclusively prove the amount of benefit provided by ECMO support in the infant with CDH.

### Type of ECMO in CDH

Traditionally, infants with CDH who require ECMO support have been preferentially placed on venoarterial (VA) ECMO. This requires ligation of the common carotid artery as well as the internal jugular vein. This practice was based largely on the belief that these infants are hemodynamically unstable and will not tolerate venovenous (VV) ECMO, as it does not provide hemodynamic support. Additionally, concerns about inadequate venous drainage and lower maximum oxygen delivery when compared with venoarterial ECMO further reinforced the notion that VA ECMO is the mode of choice in infant with CDH. However, several studies have shown VV to be an acceptable initial mode of ECMO for infants with CDH. Cornish and coworkers showed that infants with severe respiratory failure and resulting circulatory compromise were effectively supported with VV ECMO. Heiss showed similar results in infants with CDH on ECMO. Dimmit and coworkers reviewed ECMO registry data for infants with CDH and found a widespread use of VA ECMO in CDH. However, their analysis showed that VV was as effective as VA ECMO in infants with CDH. Interestingly, they found a higher incidence of seizures and cerebral infarction in infants undergoing VA bypass. In a single center study, Kugleman and coworkers also showed no difference between infants treated with VV when compared with VA ECMO for CDH. Based on concerns about inadequate venous drainage and the need to convert to VA ECMO in right-sided hernia, there has been a bias to place such infants on VA ECMO. However, Dimmitt also found no difference between right- and left-sided hernias when it comes to failure of VV ECMO and the need for conversion to VA. Furthermore, infants who did fail VV and had to be converted to VA ECMO did not have a worse outcome than those who were placed on VA ECMO initially. Based on these studies, it would be prudent to assume that most infants with CDH can be treated with VV ECMO if an adequate VV cannula (such as a 14 Fr) can be placed. Interestingly, Frenckner and colleagues found that infants with CDH tend to have smaller veins than other infants, which would make VV ECMO more difficult. However, it is not clear if this has played a role in the progressive increase in the use of VA ECMO in CDH over the years. Dimmitt and coworkers also concluded that there is a strong institutional bias when choosing VA over VV ECMO.

### CDH Surgery on ECMO

With the evolution of ECMO as a component of preoperative stabilization, the question of optimal timing to repair the defect surfaced. Operations on ECMO are a high risk procedure because of potential for anticoagulation-induced bleeding complications. Early reports of surgical repair on ECMO demonstrated a high incidence of significant hemorrhagic complications. Infants who developed significant hemorrhage on ECMO often did not survive. However, studies have shown that operations can safely be performed and significant bleeding can be avoided as long as circuit coagulation status is monitored closely. Aminocaproic acid, an inhibitor of fibrinolysis, has been has been used in ECMO patients that are at high risk for bleeding, such as those undergoing surgery. In a study by Downard and coworkers, aminocaproic acid was found to be beneficial in those patients who underwent CDH repair on ECMO. In this study, only 5% of infants treated with aminocaproic acid required re-exploration for bleeding on ECMO as opposed to 26% of patients not treated with aminocaproic acid. Many centers now use ami-

### Table 2 Criteria Used to Exclude ECMO in Infants with CDH

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<th>Reference</th>
<th>Exclusion Criteria</th>
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<tr>
<td>Boloker, et al.</td>
<td>Failure to maintain preductal saturations &gt;85% for at least 1 hour with maximal support</td>
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<tr>
<td>Heiss, et al.</td>
<td>Highest post ductal PaO2 &lt; 50 mm Hg or highest preductal PaO2 &lt;100 mm Hg</td>
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<tr>
<td>Vd Staak, et al.</td>
<td>Highest preductal PaO2 &lt;80 mm Hg</td>
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<tr>
<td>Stolar, et al.</td>
<td>Highest preductal PaO2 &lt; 100 mm Hg</td>
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nocaprio acid in addition to stricter control of circuit coagulation status for infants undergoing surgery for CDH on ECMO. Since this is an inhibitor of fibrinolysis, the potential complication of the use of aminocaproic acid is increased clot formation and a need to change the ECMO circuit more frequently due to clotting.

It is unclear what the optimal time for repair of the CDH once an infant is on ECMO support. This question has not been critically analyzed, and as a result there are significant center variations. Data from the CDH Study Group show that, of the infants that are placed on ECMO before surgery, 54% were repaired on ECMO as opposed to 30% after ECMO. Another 16% of the infants were placed on ECMO but never underwent repair, and all died. Eighty-three percent of the infants who underwent repair after ECMO survived as opposed to only 49% when repaired on ECMO. Additionally, the length of stay was shorter (64 versus 76 days) and need for oxygen lower (56% versus 64%) among infants repaired after ECMO when compared with those who were repaired on ECMO. This would be expected since those infants who could come off bypass would be expected to do better than those who could not. In those patients who did undergo repair on ECMO, the timing of operation was quite variable and ranged from repair in the first 24 hours on bypass to over 3 weeks. Not surprisingly, infants who were repaired extremely late had a worse outcome.

Long-Term Outcome of Infants with CDH Treated with ECMO

As described by West and Wilson, significant pulmonary, gastrointestinal, cardiac, and neurological morbidity has been reported in infants with CDH. The ECMO-treated infant has a much higher risk of morbidity. Stolar and coworkers found that 89% of infants treated with ECMO for indications other than CDH were cognitively normal. In contrast, only 60% of infants with CDH who were treated with ECMO had a normal cognitive examination. McGahern and coworkers, in a review of their center experience, showed a survival rate of 75% among infants with CDH that were treated with ECMO, of whom 67% exhibited signs of neurological compromise. Authors also found that infants with CDH treated with ECMO had lower Apgar scores, increased need for a diaphragmatic patch, and were more likely to require a gastrostomy tube with or without fundoplication. Based on these findings, authors conjectured that the worsened neurological outcome may be a function of severity of the illness, although independent ECMO factors could not be excluded. Analysis of ECMO registry data shows an overall survival rate of 52% for infants undergoing ECMO for CDH, but the long-term outcome for this specific group of patients has not been studied. The UK Collaborative ECMO Trial Group reported the follow up at 4 years of age for infants with CDH that were included in the original trial. There were initially 4 survivors in the ECMO group, but at follow up, 1 had died and another had severe disability. However, there were no survivors in the control group. A recent report reviewed data for all infants with CDH treated with ECMO in the United Kingdom between 1991 and 2000. Infants were followed for an average of 67 months. During this period, 73 infants with CDH were supported with ECMO. Of these, only 46 were able to wean off ECMO, 42 survived to hospital discharge, and only 27 survived 1 year or longer. Of the 27 survivors, only 7 infants were problem-free. These are sobering numbers and add fuel to the growing uncertainty about the true utility of ECMO in CDH. Additionally, Steven and coworkers found that over time, the duration of ECMO and the number of complications have increased progressively.

The reason for this change is not clear, but the authors conjectured that perhaph improvement in ventilator strategies is leading to the sicker infants being selectively placed on ECMO and hence the longer runs and more complications.

These observations should lead to renewed effort toward redefining the role of ECMO in CDH. Specifically, better selection criteria that can be used in a timely manner are likely to improve the survival and morbidity rates for these patients. It is likely that ECMO is of some benefit in a select group of patients, but until such time that selection criteria can be better clarified, the role of ECMO in CDH will remain poorly defined.

References
30. West SD, Wilson JM: Follow up of infants with congenital diaphragmatic hernia. Semin Perinatol, in press