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Congenital Diaphragmatic Hernia: State of the Art Reconstruction- Biologics Versus Synthetics

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1. Introduction

1.1 Impact of therapeutics on survival

Survival rates to hospital discharge for a neonate with a diagnosis of congenital diaphragmatic hernia (CDH) appear to have improved remarkably when comparing reports of 82-93% survival out of single institutions to the overall survival rate of 69% from tertiary centers in the Congenital Diaphragmatic Hernia Study Group (CDHSG). Others continue to dispute such outstanding gains, attributing them both to patient recruitment and a case selection bias at tertiary referral centers (Stege et al., 2004). In contrast, significantly lower survival rates of 54-56% have been reported from population-based studies in the UK and Australia despite their implementation of the same strategy of presurgical stabilization, permissive hypercapnea and gentilation with high frequency ventilator modes (Levison, 2006). Population based studies typically include more nonsurvivors than tertiary referral centers who capture only those who survived to arrival the other caveat is how to best track all those diagnosed prenatally.

The UK and Australian experience was similarly reflected in a US population-based study using the KIDS' Inpatient Database, in which overall survival was 66% (Sola et al., 2010). Strikingly, the postoperative survival in the KIDS' Database was much higher at 86% which reflects the degree of case selection bias involved in those offered surgical repair. This discordance supports those who argue the higher survival reports out of single institutions often reflect an underlying unintended case selection bias. Despite all the advances in intensive care management of diaphragmatic hernias and ventilation of critically ill neonates, there remains a >35% of live-born infants with a CDH who do not survive to transport, making the diagnosis of CDH accountable for >1% of all annual infant mortality (Clark et al., 1998) and the highest in-hospital neonatal mortality of all birth defects (CDC, 2007).

Clearly a subset of children with CDH remains predisposed to fatality despite the availability of novel therapies. Thus being able to predict which subset is most likely to

benefit from experimental or more aggressive therapies, as well as the consideration of withdrawal of care when suitable, would be remarkably useful to best target novel therapeutics for best benefit. In fact now there are many novel therapies directed at the high risk subset and liberally utilized given the inability to risk stratify patients. These novel therapeutics include the selective use of ECMO (Khan & Lally, 2005), pulmonary vasodilators such as inhaled nitric oxide (Okuyama et al., 2002; Finer & Barrington, 2001), and sildenafil (Hunter et al., 2009), permissive hypercapnea and high frequency oscillatory ventilation (Miguet et al., 1995), treatment at high volume centers (Stege et al., 2004), fetal surgery/ tracheal occlusion without proven survival advantage (Harrison et al., 2003), and the futuristic application of partial liquid ventilation (Hirschl, 2004). Other therapies often utilized, such as the use of exogenous surfactant, have not been shown to improve survival rates in the premature infant with CDH; although, they have not been analyzed in a randomized control trial to fully prove efficacy (Lally et al., 2004).

2. Defect size: Prognostic relevance

The coexistence of marked pulmonary hypertension and pulmonary hypoplasia are the key factors identifying the subset of infants that are more likely to die or survive with significant morbidity. The ability to identify prenatally those with problematic pulmonary hypertension and hypoplasia has not yet been realized. There are many indirect metrics for prenatal predictors of mortality which at best can estimate postnatal outcomes with variable accuracy. Those prenatal predictors of mortality include fetal liver position (Kunisaki et al., 2008; Kitano et al. 2005; Hedrick et al., 2007), fetal lung volumes (Nishie et al., 2009) and lung area-to-head ratios (LHR) (Bretelle et al., 2007; Deprest et al., 2009). Notably all of these measures are proxies for the severity of underlying pulmonary hypoplasia secondary to the degree of visceral herniation. In an isolated left CDH, liver position is the best prenatal predictor of outcome. In those with liver up, ECMO was required in 80% of fetuses compared to 25% for those with liver down: survival rate was 45% for the liver up subset, compared to 93% for those with liver down (Hedrick et al., 2007). In similar fashion, a low LHR (<1.0) predicted an increased incidence of ECMO (75%) with a lower survival rate (35%) (Hedrick et al., 2007), but the LHR was not useful in those <24 weeks GA (Yang et al, 2007). There are other factors used to predict survival which include birth weight >2.5 Kg (Casaccia et al., 2006), and coexistence of chromosomal and cardiac anomalies (Graziano et al., 2006; Witters et al., 2001; Hilfiker et al., 1998). The most common chromosomal anomalies identified in CDH were trisomies 13, 18, and 21, the most common syndrome was Fryns syndrome, and either a hypoplastic left heart syndrome, coarctation of the aorta, or tetralogy of fallot for the complex heart disease identified.

The size of the defect is the best corollary for the degree of pulmonary hypoplasia. *In vivo* CDH animal models have demonstrated the association between varying the size of the defect and the resultant degree of pulmonary hypoplasia in both lambs and toxicological rodent models, where the gestational timing of the insult is the factor determining defect size and outcome (Hilfiker et al., 1998). The CDHSG identified the size of the diaphragmatic hernia defect as the major factor influencing outcome based on a 9 year multi-institutional registry of 3062 CDH patients (Lally et al., 2007). Notably those with a primary repair had a 95% survival rate compared to those requiring a patch repair at 79%

in contrast to an overall survival rate of 69% for all comers. Thus a patch repair has become synonymous with larger defect sizes. Among those requiring a patch repair, those with the largest defect possible - diaphragm agenesis, had the worst odds of survival at 57% with an odds ratio of 14.04 times the mortality of those who underwent a primary repair (Singh et al., 1999). Neonates with a diaphragm agenesis are well known to be associated with a high mortality (Brindle et al., 2011).

The significance of the diaphragm defect was confirmed by the Canadian Pediatric Surgery Network (CAPSNet) in a 5-year 212 patient database which showed that a patch repair was the only significant predictor of mortality with an odds ratio of 17:1 (Skargard et al., 2005). Those requiring patch repairs were independently associated with secondary morbidities such as the number of ventilator days and the need for oxygen at discharge. The Canadian study was illustrative given the absence of other confounding variables to which to attribute the mortality risk. The subset requiring a patch repair did not also have a higher incidence of other risk variables such as birth weight, gestational age, or the presence of cardiac or chromosomal anomalies. Instead in CAPSNet, those requiring a patch repair differed from those not requiring a patch repair strictly only by their need for ECMO and SNAP-II score, both measures of disease severity. The SNAP-II score, the score for neonatal acute physiology, is a well described and validated metric for the predictor of mortality in CDH. Thus the need for a patch repair is our best proxy for defect size, and by showing a higher mortality risk associated with patch repair , defect size is the best surrogate marker for the severity of pulmonary hypoplasia.

The spectrum of defect sizes parallels the prenatal timing of initial detection prenatally and the underlying degree of associated pulmonary hypoplasia. Prenatally the degree of visceral herniation has been a good proxy for the size of the defect: the grade of herniation of the stomach into the chest (Kitano et al., 2011), herniation of the liver into the chest (Mullassery et al., 2010), herniation of the liver combined with the LHR for prediction of ECMO usage and mortality (Hedrick et al., 2007). All these prenatal measurements are used as predictors of outcome and are the best proxies for the size of the defect and the severity of underlying pulmonary hypertension. The converse is also true that there is a subset of left sided CDH neonates who have no evidence of visceral herniation *in utero* and have a remarkably higher survival rate, lower prosthetic graft rate, and lower ECMO utilization compared to the control group (Valfre et al., 2011). This finding documented what was well recognized clinically - that the presentation of a CDH postnatally is associated with smaller defects, a lower need for prosthetic graft repairs than those who present early in gestation, and better outcomes. To date the actual defect size remains immeasurable by prenatal or postnatal imaging. Although defect size is singularly predictive of outcome in both overall survival (Singh et al.,1999; Skargard et al., 2005) and longterm morbidities (Raval et al., 2011), such as gastroesophageal reflux, altered pulmonary function and poor auxological outcomes, a numeric value for the defect size has not been accurately recorded in most studies or tracked in registries. Similarly there is no identified cut-off value that defines the large defects or agenesis. Efforts continue to focus ideally on attempting to determine defect size prenatally or preoperatively to risk stratify patients and better match high risk patients with high risk therapies, with improved counseling and avoiding risky therapies in low risk patients.

3. Patch repairs: Synthetics versus Biologics

3.1 Primary repair

Primary repair is the desired standard for the closure of the diaphragmatic defect. Due to all the advances above, the cohort of more complicated repairs is increasing and long term follow up is available on the durability of various types of repair. In all cases, closure needs to ensure durability to best avoid re-herniation since re-operative surgery is not trivial in these children. The percentage of neonates undergoing repair is not clear, since different centers vary as to patient recruitment and which patients are deemed unsalvageable for surgical intervention. Not all such patients are included in registries. For an approximate estimate of the percentage repaired, analysis of the KIDS' Inpatient Database limited to all patients less than 8 days of age admitted to any hospital with a diagnosis of CDH identified 2774 patients, of which only 1095 underwent operative repair (Sola et al., 2010). Thus approximately a third of all neonates with a CDH are offered surgical repair. This analysis that a third were actually offered surgical repair was confirmed by a different KIDS' Database analysis (Raval et al., 2011). Thus not all CDH neonates are offered repair, which implies those that are offered repair represent a case selection bias. In contrast, the CDHSG registry with 3062 live born CDH infants from tertiary institutions reported a larger percentage of up to 82.4% of those tracked in the registry were surgically repaired: 43% had a primary repair, 22.1% had a patch repair and 15% had complete agenesis (Singh et al., 2009).

3.2 Synthetic and biologics

Given the expected variations of surgical preference in determining whether a patch is used, there is a trend to liberally use patches to avoid tension and compartment syndromes (Loff et al., 2005; Bax and Collins, 1984). So some elect patch repair to improve physiologic results and others use patches only when primary repair cannot be physically achieved. Current practice is to create a tension-free closure such that prosthetic patches are used only when a defect is not amenable to a primary repair, after mobilizing the posterior diaphragmatic leaf, or as in cases of agenesis. The most common material used in prosthetic patches is polytetrafluoroethylene (PTFE: Gore-tex® [WL Gore and Associates, Flagstaff, AZ]); other prosthetic materials have included composite grafts with Goretex®, SILAS-TIC© (Dow Corning, Midland, MI), Dacron, polypropylene and fluorinated polyester but none of these have been used as frequently as Gore-Tex. The concern with prosthetics is their inability to accommodate thoracic growth leading to chest restriction, chest wall deformity (Greig & Azmy, 1990), and reherniation (Hajer et al., 1998). PTFE induces no tissue ingrowth and incites a high inflammatory response with essentially no biologic fusion to the surrounding diaphragmatic muscle.

Numerous biologics have been applied to CDH defects to create a lattice, allowing for tissue ingrowth of autologous tissue (see Table 1). Biologics ideally, with tissue incorporation, would be able to avoid the reherniation rates characteristic of prosthetic patches and the scoliosis from the inability of a prosthetic to compensate for age-related growth of the thoracic cavity. The most commonly used acellular bioprosthetic patches include Surgisis-Gold (Cook Biotech, Lafayette, IN), Permacol (Tissue Science Laboratories Inc, Andover, Mass), Alloderm (LifeCell Inc, Branchburg, NJ), or recent composites with a synthetic sandwiched as an overlay to a bioprosthetic, such as Gore-tex® and Surgisis®(See Figure

1D) Prior bilayer patches incorporated both Gore-tex® and Marlex® which demonstrated only one recurrence (3.5%) (Riehle et al., 2007) which suggested a benefit of sandwiching a synthetic with a monofilament mesh to induce tissue incorporation.

Bioprosthetic	Source	Matrix	Company
Surgisis	**Porcine**	Non-crosslinked acellular small intestinal submucosa 8-ply	Cook biotech, west lafayette, ind
Permacol	**Porcine**	Chemically cross-linked acellular dermal collagen	Tissue science laboratories, ndover, mass.
Alloderm	**Human**	Non-crosslinked acellular dermal matrix	Lifecell, inc. branchburg nj
Peri-guard	**Bovine**	Chemically cross-linked pericardium	Synovis surgical innovations, st paul, minn
Veritas	**Bovine**	Non-crosslinked pericardium	Synovis surgical innovations, st paul, minn

Table 1. Types of bioprosthetic materials for grafts

Synthetic patch repairs emerged historically as the predominant method of tension-free closure of defects not amenable to primary repair (Levison et al., 2006). Despite three decades of experience with synthetic patches, which offer a superb short term solution, recurrence rates are reported as high as 41% -46% at a median follow up of 12 months (Moss et al., 2001; Jancelewicz et al., 2010), compared to 10-22% rate following primary closure in long-term survivors (Jancelewicz et al., 2010; Cohen & Reid, 1981). Long-term studies showed that prosthetic grafts can result in recurrences in up to 50% of patients by 3 years of age (Moss et al., 2001). The risk factors associated with an increased risk of recurrence in graft repairs include all factors discussed earlier that are associated with a worse disease severity, such as right side CDH laterality, ECMO therapy, size and need for a patch (Hajer et al., 1998).

Only the history of a patch repair was independently predictive of a subsequent diaphragmatic hernia recurrence when compared to multiple prenatal markers of CDH severity in a multivariant regression analysis (Jancelewicz et al., 2010). The higher rates of recurrence in synthetic patch repairs are thought to be secondary to a lack of tissue incorporation and inability to accommodate growth, so that tension over time causes the patches to separate from the thoracic wall as well as lead to chest wall deformities. Notably there is an increased prevalence of chest deformities in 50% of patients by 3 years of age, equivalent to the incidence of recurrences (Vanamo et al., 1996). In fact there is a bimodal distribution of recurrences with Gore-Tex®: an early peak at 2 months and a later peak at 20 months (Moss et al., 2001). This bimodal distribution of graft failure has been confirmed in other studies (Mitchell et al., 2008).
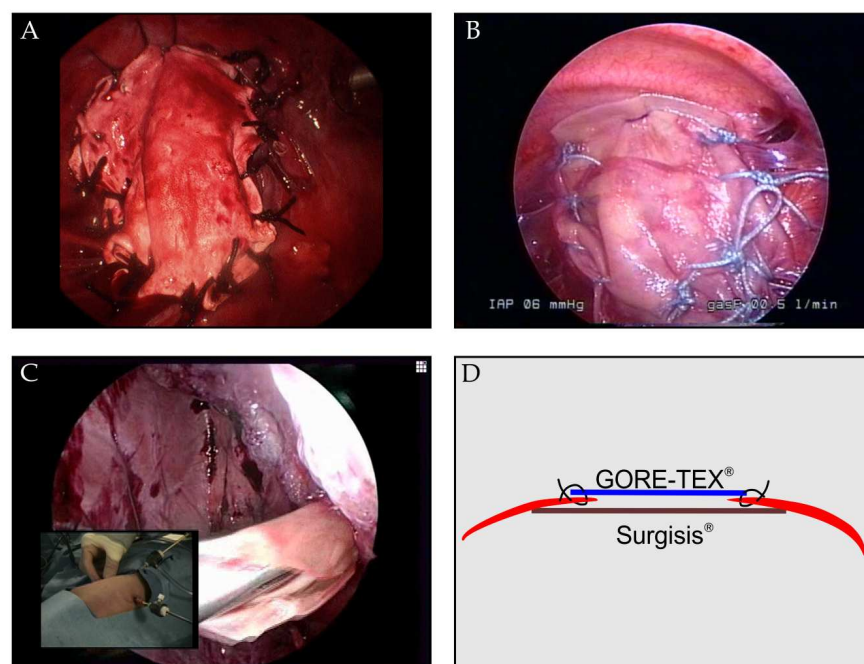
Fig. 1. Comparison of Gore-tex® and Surgisis®. A. Gortex patch sewn in situ, B. Thoracoscopic view of Surgisis® patch in situ. C. Technique of thoroscopically introducing a patch, D. A modified patch combining Gore-Tex (nonabsorbable mesh) and Surgisis (biodegradable prosthetic material) as a bilayer composite graft. (Courtesy of Dr. Mark Wulkan at Emory University School of Medicine & Emory Children's Center)

Bioprosthetics have been widely applied and successful in a variety of hernia repairs and closures of abdominal wall defects. They provide a temporary acellular scaffold that supports native tissue ingrowth and ability to accommodate growth. Since these bioprosthetics are acellular, they are nonimmunogenic. Given the high recurrence rates associated with Gore-Tex®, one study compared Surgisis® (a 4- or 8- ply porcine-derived extracellular matrix from small intestine submucosa) to Gore-Tex® in 72 newborns, reporting no significant difference in recurrence rates (38% and 44%, respectively: Grethel EJ et al., 2006). Graft failures occurred early with 92% of Surgisis® failures and 75% of Gore-Tex® failures within 1 year. A Surgisis® repair was associated with higher frequency of operative bowel obstruction, (Jancelewicz et al., 2010; St. Peter SD et al., 2007) and was possibly proinflammatory (Baroncello JB et al., 2008). In a recent *in vivo* porcine model, Surgisis® resulted in better tissue integration than PTFE, enhanced incorporation of skeletal muscle in replacement of the acellular graft with higher collagen-forming fibroblasts, and lower fibrotic reaction (Gonzalez et al., 2011). In contrast, PTFE induced a thick fibrotic capsule consistent with an inflammatory reaction that exceeded that of Surgisis®. Perforated and 8-ply Surgisis® is currently being trialed in composite grafts with Gore-Tex® (Fig 1). Remodeling of collagen-based patches in CDH applications has been analyzed in animal models to compare Surgisis®, a porcine intestinal submucosa to Gore-Tex® (Lantis et al., 2000). The collagen-based repairs showed more integration, increased vascularization, fibroblastic ingrowth, and less inflammation compared to the high inflammatory reaction at the PTFE-diaphragmatic interface. This proinflammatory reaction along the synthetic to diaphragm interface may explain the recurrence rates seen.
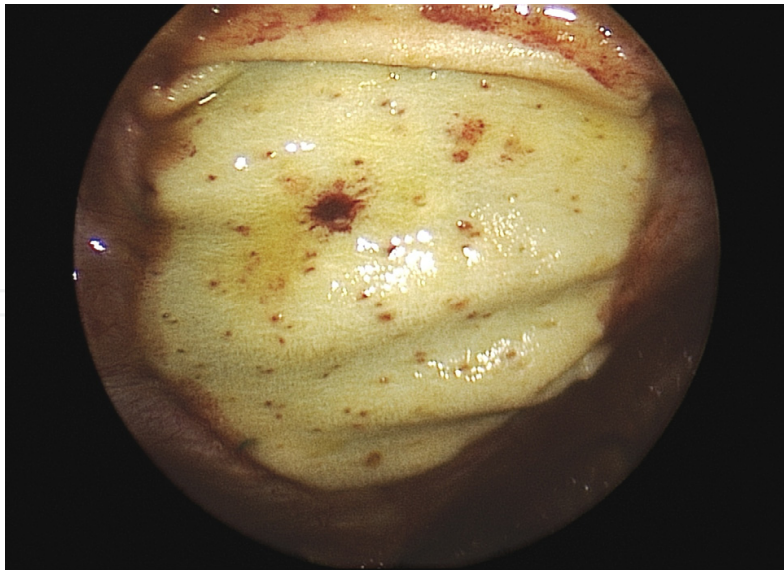
Thoroscopic view of a Permacol Patch in CDH repair.

Fig. 2. Intrathoroscopic Visualization of a Permacol® patch used in a neonatal CDH repair 2 months after placement to show tissue incorporation

Permacol®, less widely used in CDH applications but popularized in adults, is an extracelluar matrix of chemically crosslinked porcine dermal collagen. In a case report of abdominovisceral disproportion and a retrospective CDH series, Permacol® demonstrated durability with no recurrences in a median follow up of 20 months, the time frame in which Gore-Tex® demonstrated a 28% failure rate (Richards et al., 2005; Mitchell et al., 2008). The type of tissue incorporation with Permacol® is illustrated in Figure 2 above, in a baby 2 months following a CDH repair with Permacol. This is an intrathoroscopic caudal view at the diaphragm due a second surgery for a previously unrecognized lung anomaly; no suture line is evident here which is so evident with the use of a synthetic. Also there are multiple areas of tissue ingrowth from the side of the Permacol against the liver (note red punctate areas as islands of tissue ingrowth). The cross-linking of lysine and hydroxylysine residues within the collagen fibers of Permacol® imparts a higher resistance to collagenases and improved durability compared to other bioprosthetics (Richards, et al. 2005).

Composite patch repairs, such as Gore-Tex®/Marlex synthetic patches, have been reported used in humans with only a 3% recurrence rate, followed for a median of 47 months, but had an unusual comorbidity of a 17% splenectomy rate which is nontrivial in this population (Riehle et al., 2007). The search for an ideal material for CDH repairs is an ongoing active area of investigation. Clearly controlled trials are needed to compare the outcomes from composite grafts (such as Gore-Tex® with a bioprosthetic) to other bioprosthetics and synthetics; likewise bioengineered grafts are potentially promising.

3.3 Autologous grafts

Autologous tissue is often limited in size and viability in a neonate, as well as problematic given the heparinization needed for possible ECMO. Often autologous tissue is not ideal for initial repair. Thus, autologous tissue is used for more often in the setting of staged repair, recurrent reherniation or when a child is older and the tissue is more robust or of sufficient size. The first patch repair described for a CDH repair used autologous tissue and a split

abdominal wall muscle flap (Simpson & Gossage, 1971). The split abdominal wall muscle flap was idealized to place a *vascularized* and *innervated* tissue flap repair that will both accommodate growth and cover a large diaphragmatic defect. This flap has not been popularized and thus remains as infrequently used option. A single institution series retrospectively reviewed their use: in 13 patients, 5 of which were done on ECMO, there were no recurrences in 6 years excluding the one patient dying in the ECMO subset from right heart failure (Brant- Zawadzki et al., 2007). The muscle flap has yet to gain widespread acceptance as a first- line procedure (Nasr et al., 2010) and is often reserved for an older child with greater muscle capacity and robustness (Masumoto et al., 2007).

Type of graft	Pros	Cons	Citations
Anterior abdominal wall muscle flap	Primary repair	Abdominal bulge	Nasr 2010, Scaife 2008, Simpson & Gossage, 1971
Reversed latissimus dorsi muscle	Innervated, wide flap	Staged repair	Sydorak 2003
Free fascia lata repair	Strongest fascia	Loss of extremity function @ harvest site, hematoma	Sugiyama 2011, Clark 1998

Table 2. Autologous muscle or fascial flaps

Other autologous grafts are utilized for the repair of the recurrent CDH and include the reversed latissimus dorsi muscle flap (Sydorak et al., 2003); and the free fascia lata repair (Sugiyama et al., 2011). The reversed latissimus dorsi muscle flap is both vascularized and innervated and has shown promise in 7 patients with no reherniation in a medium follow up of 24 months (Sydorak et al., 2003). This use of autologous tissue is best utilized for the repair of recurrences, and allows not only a pleuroperitoneal separation, but also a potentially functional diaphragmatic reconstruction: this later point needs to be proven in longterm studies given the neural anastomosis. The free fascia lata graft has the potential of using the strongest fascia but may result in loss of extremity function, is not innervated, and its application in children or neonates is not well popularized. All autologous tissue repairs can be problematic if utilized in the setting of a heparinized circuit such as ECMO, particularly with a large surface area of dissection with associated tissue edema. All of these autologous grafts are cautioned to be used with a liberal application of a staged abdominal wall closure, particularly in those on ECMO support with resultant significant tissue edema.

4. Impact of minimally invasive surgery on recurrences

The revolution in minimally invasive surgery (MIS) naturally allowed the application of MIS to the repair of CDH patients. Theoretically, a minimally invasive repair would minimize the deleterious effects of open surgery while being able to decompress the CDH lung. Many reports have proclaimed the feasibility and initial safety of MIS in its application to CDH repairs (Yang et al., 2005; Shah et al., 2009).

Since the technique is relatively new, there was a careful case selection bias in order to select those patients most suitable. Despite a case selection bias, there is already a significant incidence of recurrences in those repaired by MIS, as opposed to those undergoing an open repair, when examining 151 MIS repairs in the CDH registry out of a total of 4516 patients repaired (Tsao & Lally et al., 2011). Case selection was intended and evident in the disparate use of ECMO (Cho et al., 2009) and targeting groups with favorable criteria such as ventilator stability and absence of stomach or liver herniation (Yang et al., 2005; Kim et al., 2009). Thus, the higher in-hospital recurrence rates will need to be analyzed over longterm to evaluate outcomes. A meta-analysis of thoracoscopic neonatal CDH repairs illustrated that a thoracoscopic repair is associated with a 3-fold increased recurrence rate and longer operative times, although the mortality rate was similar in open and thoracoscopic repairs (Lansdale et al., 2010). Potentially, the thorocoscopic approach does not allow sufficient mobilization of the posterior leaflet of the diaphragm, committing more patients to prosthetic graft repairs overall.

5. Conclusion

In summary given the heterogeneity of disease severity, the complexity of CDH repairs has not been able to be prognostically separated into clear risk-stratified groups preoperatively to appropriately match for the therapies best suited to a category of risk. Now that the relationship of defect size to incidence of patch severity has been established, it is clear that many strategies are needed to best benefit those with the greatest defects and the worst CDH severity, both in the short term and long term. Composite bioprosthetic grafts and biologics have shown promise.

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