



## Permacol: a potential biologic patch alternative in congenital diaphragmatic hernia repair<sup>☆,☆☆</sup>

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### Abstract

**Purpose:** Recurrence is a well-known complication after patch repair of congenital diaphragmatic hernia (CDH). We propose that a newer, “bioprosthetic” material may lower recurrence rates. The purpose of this study is to compare outcomes of CDH repair with synthetic Gore-Tex (W. L. Gore and Associates, Neward, Del) to the bioprosthetic Permacol (Tissue Science Laboratories Inc, Andover, Mass).

**Methods:** We performed a retrospective review of 100 consecutive patients with CDH with survival more than 30 days at Children's Medical Center of Dallas (Dallas, Tex) from 1999 to 2007. The incidence and timing of recurrence, as well as comorbidities were assessed.

**Results:** Primary repair was performed in 63 patients and patch repair in 37, divided between Gore-Tex (29) and Permacol (8). Overall recurrences were as follows: 1 (2%), 8 (28%), and 0 in the primary, Gore-Tex, and Permacol groups, respectively. Median follow-up was 57 months for Gore-Tex and 20 months for Permacol. Median time to recurrence in the Gore-Tex group was 12 months, with no Permacol recurrences. Both the Gore-Tex and Permacol groups had similar comorbidities, including prematurity, congenital heart disease (76% and 63%, respectively), and the need for extracorporeal membrane oxygenation support (38% and 25%).

**Conclusion:** Our results suggest that Permacol may have lower recurrence rates compared to Gore-Tex and is a promising alternative biologic graft for CDH repair.

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The treatment of congenital diaphragmatic hernia (CDH) has evolved significantly for the past 3 decades, and survival rates are as high as 83% in surgically repaired patients. Recent evidence has shown that defect size correlates well with mortality and morbidity in CDH and is likely a surrogate marker for the degree of concomitant pulmonary hypertension and hypoplasia [1]. Advances in neonatal intensive care have created a cohort of patients with large defects and often significant comorbidities, who previously did not survive to repair or who died shortly thereafter. These large defects often cannot be closed primarily without undue tension, necessitating an alternative method of closure that can be performed in critically ill infants. Ideally, this repair would be both durable to prevent recurrence yet sufficiently pliable to allow the diaphragm to increase in size several-fold as the child grows.

Synthetic patch repairs have emerged as the predominant method for the closure of CDH defects not amenable to primary repair [2]. However, despite more than 3 decades of experience with synthetic patches, recurrence rates remain as high as 40% [3-6], potentially because of poor tissue incorporation and growth accommodation. Tissue remodeling studies have demonstrated the improved patch integration and decreased inflammatory response of collagen-based "bioprosthetic" patches when compared to synthetic material [7]. Initial human trials of Surgisis (a porcine intestine-derived collagen mesh) (Cook Biotech Inc, West Lafayette, Ind) for CDH repair showed promise [8]; however, larger studies have demonstrated recurrence rates similar to Gore-Tex (W. L. Gore and Associates, Neward, Del) [6,9]. Permacol (Tissue Science Laboratories Inc, Andover, Mass) is a sheet of collagen derived from porcine dermis that has the further advantage of chemical cross-linking, rendering it more resistant to collagenase degradation, while retaining good tissue integration. This newer bioprosthetic has been used successfully in a wide range of applications in adults, including the closure of contaminated fields, where synthetic materials are contraindicated. In this study, we aim to compare the recurrence rates of large CDH defects repaired with Gore-Tex or Permacol.

## 1. Methods

Upon obtaining institutional review board approval, we retrospectively reviewed the medical records of all consecutive patients diagnosed with CDH between January 1999 and July 2007 at our institution. Patients who survived less than 30 days were excluded, whereas those who presented with reherniation were included. The remaining 100 patients were assessed for the mode of repair (primary vs graft: Gore-Tex and Permacol) and evaluated for the primary outcome of recurrence. There were no major differences in operative or perioperative management, and all operations were performed by our group of experienced

**Table 1** Comparison of Gore-Tex and Permacol repairs

	Gore-Tex	Permacol	<i>P</i>
Subjects	29	8	
Median F/U (IQR)	57 mo (49-73)	20 mo (9-33)	N/A
Median Age at repair (IQR)	Term (term)	Term (term)	N/A
Mean Age at repair ( $\pm$ SD)	5 mo ( $\pm$ 18.5)	0.6 mo ( $\pm$ 1.8)	.82 <sup>a</sup>
Required ECMO	11 (38%)	2 (25%)	.69 <sup>b</sup>
Cardiac Anomaly	22 (76%)	5 (63%)	.66 <sup>b</sup>
Diaphragm Agenesis	3 (10%)	1 (13%)	N/A
Recurrent Hernia	8 (28%)	None	.16 <sup>b</sup>
Median Time to Tecurrence	12 mo	None	N/A

IQR indicates interquartile range.

<sup>a</sup> Mann-Whitney test.

<sup>b</sup> Fisher's Exact test.

pediatric surgeons. Patches were placed at the discretion of the attending surgeon to avoid undue tension, and none were placed to reinforce a repair. All repairs before 2004 used Gore-Tex, whereas all except one after 2004 used Permacol. Patient groups were evaluated for demographics and comorbidities such as prematurity, the presence of cardiac anomalies, and use of extracorporeal membrane oxygenation (ECMO). Follow-up was based upon symptomatic recurrence and not sequential imaging, consistent with current clinical practice. Statistical analyses were performed using SPSS (SPSS Inc, Chicago, Ill) and used Fisher's Exact test or Mann-Whitney where indicated.

## 2. Results

A total of 116 patients presented with CDH during the 8-year study period, of which 16 survived less than 30 days, yielding a total study population of 100 patients (85% overall survival). Most patients (63%) underwent primary repair, whereas the remainder required patch repair with either Gore-Tex (29%) or Permacol (8%) (Table 1). The primary and Gore-Tex groups had similar median follow-up times (64 and 57 months, respectively), whereas the recently introduced Permacol repair had a median follow-up time of 20 months. Given the possibility of selection bias among patch repairs, the Gore-Tex and Permacol groups were analyzed for the presence of cardiac anomalies and the use of ECMO, and no significant differences were identified. There were no differences between the 2 groups with respect to median age or prematurity at the time of repair. The mean age at repair is higher in the Gore-Tex group; however, this is heavily influenced by 2 outliers and is not statistically significant by the Mann-Whitney test. Diaphragmatic agenesis, the largest defect possible, was present in 3 patients receiving Gore-Tex repairs, and one in the Permacol group, thus proportionally represented in both groups.

Although only one primary repair recurred at 6 months of follow-up (3%), 8 (28%) of the 29 Gore-Tex repairs recurred. The Gore-Tex recurrences showed a bimodal distribution, in which 5 recurred within the first 12 months of life (median, 7 months) and the remainder at 2.5, 4.25, and 4.5 years (median, 4.25 years). During the study, none of the Permacol repairs have recurred. Although impressive, these results do not reach the level of statistical significance. Of the 9 total recurrences, 7 presented with respiratory difficulties, whereas two were asymptomatic, found on imaging for other reasons. No patients in either group have presented with bowel obstruction (previously identified as an indicator of recurrence [9]), nor have any Permacol-repaired patients presented with complications related to the repair.

### 3. Discussion

Primary repair remains the gold standard for the closure of CDHs; however, many patients with large defects or total diaphragmatic agenesis require a patch closure. The first such repair was described in 1971 by Simpson and Gossage [10], using a split abdominal wall muscle flap. In the largest series of this type of closure, Brant-Zawadzki [11] reported results from 13 patients (including five on ECMO), with only one recurrence. Despite this promising data, the muscle flap technique has yet to gain widespread acceptance as a first-line procedure, often reserved as an option to treat a recurrence when patients are older, with greater physiologic reserve and muscle thickness [12].

Current practice to create a tension-free closure of large defects favors the use of synthetic Gore-Tex patches; however, recurrence rates are highly variable [2]. In 2001, Moss [5] examined a series of 45 infants with CDH who underwent Gore-Tex patch repair and noted a 41% recurrence rate at a median of 12 months follow-up. In contrast, Riehle [13] recently described a repair with a double-sided, Gore-Tex/Marlex synthetic patch with only once recurrence. Of concern, this group also noted a 17% splenectomy rate in patients requiring patch repair, a nontrivial complication in this patient population. In our series, 28% of our Gore-Tex repairs recurred with a median follow-up of 57 months, and no patient required splenectomy.

Given the difficulties seen with synthetic materials, the common “bioprosthetic” material Surgisis (non-cross-linked porcine submucosal collagen) was recently compared to Gore-Tex in 72 newborns [6]. No significant difference was found in the recurrence rate between the two (38% and 44%, respectively). Recurrence in this study was primarily an early event, as 92% of Surgisis failures and 75% of Gore-Tex failures occurred within 1 year. Moss and colleagues [5] had previously reported grouping of early and late Gore-Tex recurrences, with peaks at 2 months and 20 months. In our study, Gore-Tex recurrences have a similar bimodal distribution, with medians at 7 months and 51 months.

After 20 months median follow-up, no Permacol repair has failed—an interval more than twice the time to early recurrence in our Gore-Tex group.

Permacol is an acellular sheet of porcine dermal collagen that has been chemically cross-linked. As a “bioprosthetic,” Permacol exhibits only a modest inflammatory reaction, consistent with the normal wound healing process. This decreased inflammation may allow for better incorporation of the repair within the highly mobile diaphragm and may account for a decrease in the high early recurrence rate seen with synthetic repairs. The cross-linking of lysine and hydroxylysine residues within the collagen fibers of Permacol imparts a higher resistance to collagenases and potentially improved durability when compared to other non-cross-linked bioprosthetics. Despite the successful use of Permacol in the adult population for difficult abdominal wall closures in the presence of contamination, fistulae, and/or elevated abdominal pressures, Permacol has never been reported in the repair of CDH. Furthermore, the only published use in the pediatric age group is a single case report where Permacol was used to bridge the abdominovisceral disproportion created by an organ size disparity in a 2-year-old renal transplant recipient using an adult kidney [14].

The remodeling of collagen-based patches in CDH has also been examined in animal models. Lantis and colleagues [7] compared the use of porcine intestinal submucosa with Gore-Tex in repairing a 2 × 2-cm diaphragm defect in rabbits. At 12 weeks, the collagen-based repairs appeared much more integrated, with increased vascularization and fibroblast ingrowth. In contrast, there was a high inflammatory response at the polytetrafluoroethylene (PTFE)-diaphragm interface, as opposed to the decreased presence of inflammation in the collagen group. Permacol itself has also been compared against other bioprostheses in a rat model of both acute and chronic ventral hernia [15]. Permacol and Periguard (Synovis Surgical Innovations, St Paul, Minn) (cross-linked bovine pericardium) provided stronger, more durable repairs when compared to Alloderm (LifeCell Inc, Branchburg, NJ) (human acellular dermal matrix) and non-cross-linked bovine pericardium (Veritas, Synovis Surgical Innovations, St Paul, Minn) at 6 months. The authors noted, however, that Periguard was more prone to skin necrosis and infection, concluding that Permacol provided a more durable repair in this model.

When large CDH defects are not amenable to primary repair, Permacol appears to be a safe, durable alternative to a synthetic patch. Although this series is small, our results underscore the need for a multicenter, prospective trial to accrue appropriate patient numbers and definitively establish the use of Permacol in the treatment of such defects.

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