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Review Article

Successful Utilization of Poly-4-Hydroxybutyrate Mesh in High Risk, Complex Abdominal Wall Reconstructions with Photo-Microscopic Analysis.

Amir H Fathi MD, FACS[a], Joshua Ladella MD[a], Shabnam Pooya PhD[b], David Slater MD[c], John Bilello MD, FACS[a]

[a]*Department of Surgery, University of California San Francisco (UCSF), Fresno Medical Education program, Fresno, CA*
[b]*California State University, Fresno, Fresno, CA*
[c]*Department of Pathology, Community Regional Medical Center, Fresno, CA*

Corresponding Author Information

Amir H Fathi MD, FACS

Assistant Clinical Professor of Surgery, Department of Surgery, University of California, San Francisco, Fresno Medical Education Program. Address: 2335 E. Kashian Lane, Suite 220, Fresno, CA 9370, Tel: 858-207-7064.

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ABSTRACT

Background: Biosynthetic resorbable mesh offers encouraging alternative for reinforcement in complex hernia repairs. This study evaluated outcomes of P4HB, absorbable polymer scaffold, in high-risk patients undergoing complex abdominal hernia repairs.

Materials and Methods: This is a retrospective outcomes analysis of a prospectively kept database. Patient/wound characteristics, perioperative findings, short/mid-term outcomes of our cohort were analyzed. Endpoints included hernia recurrences, wound events and any complications. ACS NSQIP online risk calculator was used for each patient to obtain predicted outcomes as virtual matched control group. We also performed a full-thickness abdominal wall biopsy at 14-months post mesh implantation for histologic evaluation.

Results: 28 patients with mean age 57 years and mean BMI 31 were analyzed. 21 patients (75%) had preexisting infections. 20 (71%) of patients had class I wounds per CDC classification at time of surgery. However, 19 of these 20 had wound or deep organ/space infections prior to surgery. Repair types included restoration of Linea Alba with retromuscular mesh placement in 23 patients (82%) with 22 of them requiring additional myofascial release. 5 patients (18%) had only mesh placement. Postoperatively, 11 patients (39%) had complications with zero hernia recurrence and zero mesh explantation at maximum of 42 months of follow up.

Conclusion: P4HB can be successfully used in high-risk operative fields with no postoperative mesh explantation, despite serious complications such as infected hematomas. Histologic evaluation of the human tissue, 14-months post-implantation of P4HB confirms mesh presence with surrounding dense collagen scaffold formation and minimal inflammatory response.

Introduction

Mesh reinforcement has been recognized as the standard of care in vast majority of ventral hernia repairs. This pattern of practice has been adapted from clinical trials performed in clean ventral hernias cases, considering the integral role of mesh reinforcement in reducing hernia recurrence rates [1-5]. However, for high risk, contaminated cases, the literature lacks large randomized controlled trials and comparative data to guide the choice of appropriate enforcement type and closure technique [5].

Use of mesh in contaminated cases has been shown to be associated with an increased risk of infectious complications such as surgical

site and deep organ space infections [6]. To overcome this problem, biologic prosthetics were introduced over a decade ago, which were considered to be significantly beneficial in the clearance of infection in clean-contaminated and contaminated wounds [7-9]. Despite the initial promise of biologic prosthetics, there has been mounting data questioning their long-term efficacy and biologic characteristic benefits in high risk cases. Although the pendulum of mesh selection appears to be swinging away from biologics, over 90% of surgeons today still prefer some form of biologic prosthetic in their complex abdominal wall hernias [10].

Absorbable synthetic meshes, which remodel via vascular integration and resorb predictably via hydrolysis, have been developed as a potential alternative to biological meshes. These new biosynthetic meshes are manufactured using polymers and are designed to gradually absorb into the host tissue, transferring strength from the mesh to the tissue. This is achieved by an ingrowth of collagen across the defect, a feature not observed in other meshes [10]. Currently, there are over five different types of biosynthetic meshes that are being promoted, differing in origin, tensile strength and degradation properties [11]. One such bioabsorbable synthetic material used for biosynthetic meshes is transgenic *E. coli*-derived poly-4-hydroxybutyrate (P4HB). This monomer is found as a natural metabolite in many tissues including the brain, heart, liver, kidney, and muscle. P4HB hydrolyzes over 365 to 545 days into byproducts which are metabolized to form carbon dioxide and water at a physiologic pH, thereby preventing local inflammation [12].

In this paper, we seek to publish our abdominal wall reconstruction experience with P4HB mesh reinforcement in high-risk clean, clean-contaminated and contaminated wounds. Short and mid-term hernia recurrence, and post-operative complications have been evaluated in detail. Furthermore, we had the opportunity to perform a full thickness abdominal wall biopsy on one of the patients 14 months after ventral hernia repair with bilateral posterior component separation and P4HB mesh implantation. The pathological evaluation with photo-microscopic images has been shared as well.

Methods

Patient cohort

This is a retrospective study of a prospectively maintained hernia database, evaluating the short and mid-term outcomes of abdominal wall reconstructions for high-risk clean, clean-contaminated and contaminated ventral hernia repairs performed by a single surgeon between February 2016 till present (A.H.F.). This study was approved by the Institutional Review Board.

Our cohort included 28 adult patients undergoing a planned single-stage repair of their ventral hernia of at least 100 cm^2 by physical examination. Each patient had the mesh placed in a wound classified by the Centers for Disease Control (CDC) wound criteria as clean, clean-contaminated, contaminated, or infected [13]. Most of the clean cases had a prior history of infection. Repairs were also considered contaminated when synchronous enteric fistula takedown, infected synthetic mesh removal, or concomitant bowel surgery was performed.

Patient demographics and clinical data reviewed and extracted include age, sex, American Society of Anesthesiologists (ASA) score, patient comorbidities, body mass index, and functional status. We also characterized perioperative details, wound classification based on CDC guidelines, and the source of contamination. The source of contamination was categorized as gastrointestinal (GI; including biliary sources), genitourinary/gynecologic, and/or infective. Infective sources included chronic draining sinuses and wounds, with or without underlying mesh involvement, along with chronic soft tissue infection in the absence of gross purulence (representing long-term contamination or colonization) as described by Majumder et al. [7].

Primary outcomes for this study were surgical site occurrence (SSO), surgical site infection (SSI) and hernia recurrence. The definition of SSO was adopted from the Ventral Hernia Working Group definition [13]. Common SSOs following ventral hernia repair include infection, seroma, wound dehiscence, and the formation of enterocutaneous fistulae. SSIs were further categorized as superficial, deep, or organ space according to CDC criteria [13,14].

We also further analyzed postoperative outcomes to include hernia recurrence rate, length of hospital stay, 30 day readmission and reoperation rates, incidence of mesh explantation, and any complications such as serious complications. Serious complications include cardiac arrest, myocardial infarction, pneumonia, progressive renal insufficiency, acute renal failure, pulmonary embolism, deep venous thrombosis, return to the operating room, deep incisional surgical site infection, organ space surgical site infection, systemic sepsis, unplanned intubation, urinary tract infection, and wound disruption.

Typical follow-up evaluation consisted of a physical examination at 2 weeks, 1 month, 3 months, 6 months, 1 year and then annually. Mean follow up for this study was 20 months with minimum of 6 months and maximum of 42 months. The short-term hernia recurrence was determined by physical examination. Abdominal computed tomography (CT) scans were obtained if there was a concern for recurrence or complications such as deep or organ/space infection during the follow ups.

Furthermore, we have utilized the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Online Surgical Risk Calculator to estimate the chance of an unfavorable outcome after surgery for each of our patients [15]. The ACS NSQIP tool results were used as a matched virtual control and a benchmark comparison for our outcomes. The data for each patient were entered into the ACS NSQIP online tool to predict unfavorable outcomes for each patient.

Surgical Technique:

The preferred method of complex abdominal wall reconstruction was primary fascial closure after bilateral or unilateral transverse abdominis muscle release (TAR), also known as posterior component separation. This technique has been described by Novitsky et al. and has been studied extensively since then [16]. Poly-4-hydroxybutyrate, Phasix™ (Bard, Warwick, RI) mesh was placed in the retromuscular space for these cases, after re-approximation of the posterior rectus sheaths. We followed the principle of "giant reinforcement of visceral sac", described by Stoppa [17]. Therefore, the large mesh was not secured by trans-fascial sutures. In cases of abdominal carcinomatosis or cirrhosis with significant varix formation, reconstruction of the Linea Alba with onlay P4HB mesh placement technique was used. The mesh was fixed with absorbable sutures and fibrin glue to the anterior recti fascia. This technique was originally described by Chevrel [18]. Drains were routinely placed superficial to the mesh. They were removed when output was less than 30 ml/day. Antibiotics were continued for the first 24 hours according to the Surgical Care Improvement Project (SCIP) protocols.

Pathological analysis

One of our patients was admitted to the hospital with acute cholecystitis, 14 months after his index incisional hernia repair with bilateral posterior component separation and retrorectus placement of a 30x20cm P4HB mesh. Initial evaluation revealed no hernia recurrence and the patient was taken to the operating room for laparoscopic cholecystectomy. This operation was concluded laparoscopically with conventional port placement.

This case provided a unique opportunity, since along with the right upper quadrant port placement, we were able to perform a full-thickness abdominal wall biopsy to evaluate the state of the P4HB mesh and abdominal wall, 14 months post-implantation and successful abdominal wall reconstruction. The specimen was processed, embedded, sectioned at approximately 5 micromillimeters and stained with hematoxylin and eosin (H&E), trichrome stain for collagen and CD68 immunostaining (a marker for histocytes). Histologic evaluation was performed by an independent board-certified pathologist at Community Medical Centers, Fresno, CA.

Results

Perioperative Findings:

Between February 2016 and February 2018, 28 patients who underwent the complex ventral hernia repair with P4HB mesh in high-risk operative fields were analyzed. Patients' demographics, characteristics and comorbidities are summarized in Table 1. With the exception of one patient, all of the patients had prior abdominal surgeries including failed prior hernia repairs with mesh implantation. The one without surgery had alcoholic cirrhosis with portal hypertension and large varix formation, rendering a hostile abdomen. No hernia surgery was performed for patients with a BMI>40. Smoking cessation was strongly recommended prior to surgery. However, four patients refused to quit and accepted the increased risks associated with the hernia repair. In this cohort, 21 (75%) of the patients had documented prior wound or deep organ space infections such as gangrenous cholecystitis, perforated diverticulitis or infected pancreatic necrosis. 6 patients had multiple failed hernia repairs with mesh implantation, prior GI surgery, or ostomy take down at the time of our index hernia repair. One patient had cirrhosis with severe portal hypertension, as mentioned before.

Table 1: Patient Characteristics and Demographics

	n = 28
Demographics	
• **Age**	57 ± 12 years
• **Male:female ratio**	19M:9F
• **Mean BMI**	31 ± 6 kg/m^2
• **Functional status**	All independent
• **ASA score**	Class 1: 0% (n=0) Class 2: 29% (n=8) Class 3: 57% (n=16) Class 4: 14% (n=4)
Comorbidities	
• **Hypertension**	46% (n=13)
• **Diabetes mellitus**	29% (n=8)
• **Current smoker**	14% (n=4)
• **COPD**	11% (n=3)
• **CKD**	4% (n=1)
• **Chronic steroid use**	29% (n=8)
• **Prior abdominal surgery**	96% (n=27)
• **Obesity**	54% (n=15)
• **Pre-existing infection**	61% (n=17)
• **Cirrhosis**	14% (n=4)

Table 2: Perioperative Details

		n=28
CDC Wound class		Class 1: **71%** (n=20) Class 2: **11%** (n=3) Class 3: **11%** (n=3) Class 4: **7%** (n=2)
Prior infection		**75%** (n=21)
Source of contamination		GI: **18%** (n=5) GU: **0%** (n=0) Infectious: **11%** (n=3) Clean: **71%** (n=20)
Average Mesh Size	**Width (cm)**	25.7
	Length (cm)	26.2
	Area (cm^2)	732
Mesh Location		Onlay: **18%** (n=5) Retrorectus: **82%** (n=23)
Posterior Component Separation		Yes: **79%** (n=22) No: **21%** (n=6)

Table 2 shows the perioperative details for our patients. As per the CDC classification, 20 (71%) of our patients had a class I wound at the time of our hernia repair. However, 19 of this class I patients had prior wound or deep organ space infections as described above. Only our cirrhotic patient did not have any infections, hernia repairs, or ostomies in the past.

Release of the transversus abdominis muscle and posterior component separation was necessary to restore the Linea Alba in 22 of our patients. The only method was used in 5 patients with hostile abdomen, and bilateral dissection of the posterior recti sheaths without any component separation was used to close the midline fascia in only one patient. We followed the giant reinforcement of the visceral sac principle in our hernia repairs. Therefore, a relatively large piece of P4HB mesh (average mesh area of 732 cm^2) was placed for reinforcement and force distribution.

Table 3: Postoperative Findings and Outcomes

	n=28
SSI	
• **Superficial**	11% (n=3)
• **Deep**	7% (n=2)
• **Organ Space**	0% (n=0)
SSO	
• **Wound morbidity**	21% (n=6)
• **Seroma**	7% (n=2)
• **Hematoma**	7% (n=2)
• **Dehiscence**	4% (n=1)
• **Cellulitis**	4% (n=1)
Any complication	39% (n=11)
• **Serious Complication**	18% (n=5)
• **Readmission**	4% (n=1)
• **Hernia Recurrence**	0% (n=0)
• **Reoperation**	7% (n=2)
• **Mesh Explantation**	0% (n=0)

Table 4: Comparison of observed outcomes to the expected outcomes, based on the ACS NSQIP online risk calculator

	Actual Outcome	Predicted Outcome
Any Complication	39% (n=11)	18% ± 6%
Serious Complication	25% (n=7)	15% ± 5%
Surgical Site Infection	18% (n=5)	8% ± 2%
Readmission	4% (n=1)	11% ± 3%
Return to Operating Room	7% (n=2)	6% ± 2%
Duration of Stay	6 ± 3 days	5 ± 1 days

Postoperative findings:

Postoperatively, 11 (39%) of our patients had complications, including 5 (18%) serious complications. Table 3 summarizes postoperative findings and outcomes. One of our 5 onlay cases developed a seroma, requiring prolonged drainage. We had 6 wound events including 5 cases of surgical site infections and one dehiscence. One of our deep infection cases necessitated operative washout and drainage. The remainder of the wound events were managed conservatively with outpatient drainage and daily packing (Figure 1). We had two cases of infected hematomas. These hematomas formed over the mesh, beneath the recti muscles, and became infected with methicillin resistant *Staphylococcus aureus* (MRSA). In one case the infected hematoma was managed conservatively with culture guided antibiotic treatment and percutaneous drainage catheters placed by Interventional Radiology, while the other case required surgical drainage along with proper antibiotic treatment. Eventually, the hematomas were cleared with no compromise of the mesh or the hernia repair (Figure 2). As mentioned above, we had two reoperation cases with no mesh explanation.

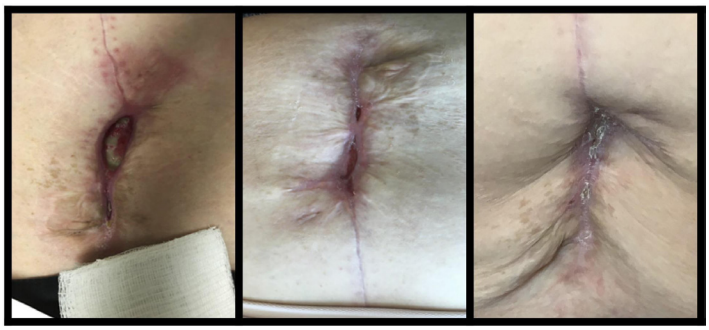

Figure 1: Progression of deep surgical site infection case, managed conservatively.

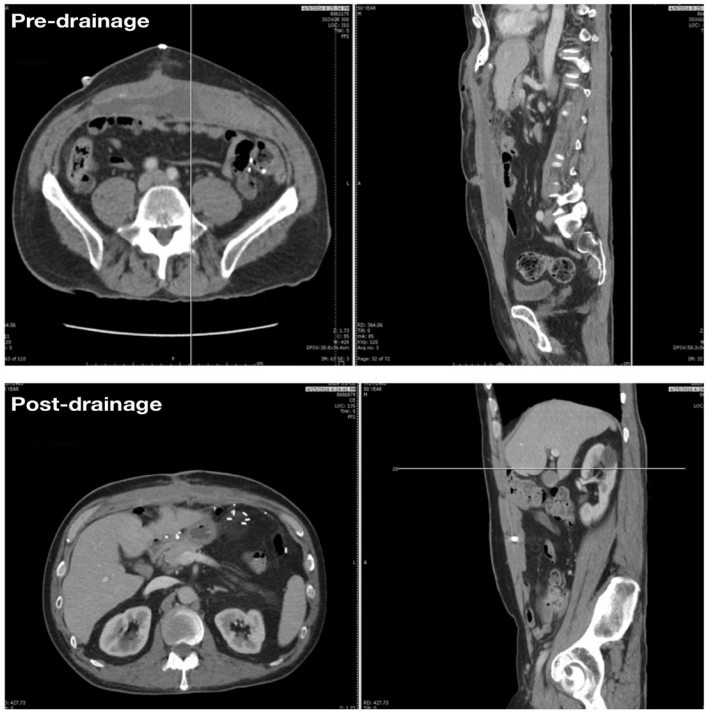

Figure 2: Infected hematoma, managed successfully with percutaneous drainage catheters and antibiotic treatment

Our follow up intervals at 2 weeks, 1 month, 3 months, 6 months, and yearly visits revealed no hernia recurrence on physical examination. The mean follows up period for this study was 20 months, with a maximum of 42 months and a minimum of 6 months. No perioperative mortality was observed as well.

Table 4 compares our observed outcomes to the expected outcomes, based on the ACS NSQIP online risk calculator. The data for each patient was entered into the ACS NSQIP online tool to predict the outcomes for each patient. Despite having a higher observed rate of any complication (39% actual vs 18% predicted) or SSI (18%

actual vs 8% predicted), our patients had a similar reoperation rate (7% actual vs 6% predicted) and a lower readmission rate (4% actual vs 11% predicted) when compared to the ACS NSQIP predictions. The average length of hospital stay for our patients was 6 days, similar to the predicted outcome of 5 days.

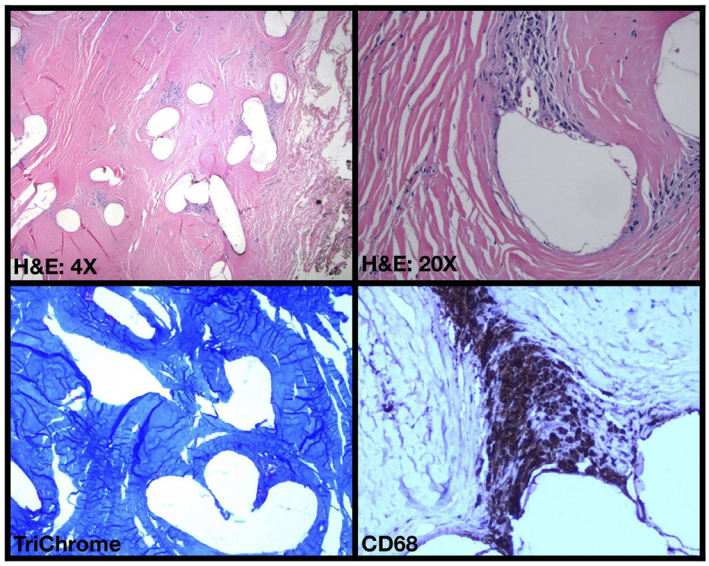

Figure 3: Photo-micrographs of P4HB mesh in full thickness abdominal wall biopsy.

Pathological analysis:

The abdominal wall biopsy measured 1.7 x 1.3 x 0.8 cm. No mesh material was appreciated grossly. Figure 3 depicts representative photo-micrographs of the biopsy. Microscopically, presence of the implant is represented by sharply punched out, round to ovoid small spaces. No actual implant strands are present after tissue processing. This indicates that the implant material has not been incorporated into or become completely adherent to the patient tissue. Therefore, it dropped out as the tissue was thinly cut for slides.

Trichrome staining shows that tissue surrounding the punched-out spaces is dense collagen and low cellularity stromal fibrosis, as seen in Figure 3. These chronic changes are consistent with the 14-month interval since implant placement. In the immediate vicinity of spaces from implant strands, there are small collections of mononuclear inflammatory cells, predominantly histiocytes as seen on CD68 immunostaining (Figure 3). Finely granular dark staining material around implant strand defects is likely remnants of inflammatory cell nuclei at the implant interface. The collagen fibrosis surrounding the spaces has accentuated vascularity, particularly in proximity to the histiocytic inflammation, as a component of the reactive process to that material. Essentially no acute inflammation is noted and no granulomas are evident.

Discussion

Abdominal wall reconstruction continues to pose challenges for surgeons around the world. Contemporary surgeons, particularly the ones emerging from training programs, are faced with different classes and multiple brands of mesh prosthetics and an abundance of variable data. Consideration of the modifiable and non-modifiable patient risk factors and hernia characteristics makes the appropriate decision-making process overwhelming at times for complex hernia repairs in high-risk patients.

For many years, surgeons have anecdotally used synthetic meshes in a variety of wounds, with variable success rates. However, the advent of biologic scaffolds within the last decade has brought a dramatic shift from synthetic meshes to biologics such as cadaveric human, bovine, and porcine driven scaffolds [10]. This shift was mainly driven by the hope to minimize the postoperative wound events for the clean-contaminated or contaminated hernias. Unfortunately, data is sparse for prospective randomized trials assessing the outcomes of hernia repairs in CDC wounds class II – IV utilizing the biologic meshes. Essentially, the Repair of Infected and Contaminated Hernias (RICH) trial is the only long-term, multicenter, prospective trial to evaluate biologic mesh in CDC class II to IV wounds. The RICH trial revealed a 66% surgical site occurrence and 28% hernia recurrence at the end of their 2-year follow-up interval in patients who underwent ventral hernia repair with a non-crosslinked porcine dermis [19]. Despite the given facts, over 90% of surgeons currently still prefer some form of biologic prosthetic in their complex abdominal wall hernias [10].

Aside from underperformance of these meshes from a clinical outcome's standpoint, they have substantially increased the cost of ventral hernia repairs as well. Reynolds et al. have shown that the median contribution margin for complicated open ventral hernia repairs with biologic mesh was –$4560, and the median net financial loss was $8370 [20].

The recent introduction of biosynthetic meshes is intended to mitigate the mentioned pitfalls. This class of meshes offers constructive remodeling, a balance between scaffold degradation and collagen deposition, with biomechanical integrity and a promise of infection resistance.

At their multicenter prospective longitudinal study (COBRA study), Rosen et al. demonstrated that the biosynthetic mesh, GORE® BIO-A® Tissue Reinforcement, performed well in the reinforcement of the midline fascial closure in the single-staged repair of contaminated ventral hernias. Overall, hernia recurrence occurred in 16 patients with a Kaplan-Meier recurrence rate of 17% at 24 months [14].

P4HB is a natural polymer derived from transgenic *E. coli*, woven into larger mesh or plugs [10]. The breakdown profile of P4HB is currently the longest of this new class of absorbable synthetic polymers. Prolonged breakdown is believed to promote slow and continuous transfer of weight-bearing tension from the graft to the native abdominal wall, allowing for collagen ingrowth [10-12].

Initial experience with P4HB by Buell et al. has shown a clear superiority over cadaveric biologic xenografts in drain removal

time, postoperative complications, and recurrent hernia formation. They have identified a dramatic and continuous remodeling and shaping of the mesh over time [10].

In this study we sought to demonstrate our limited experience with P4HB in high risk ventral hernia repairs. Our experience included 28 patients with a variety of comorbidities who have undergone complex abdominal wall reconstruction with P4HB mesh reinforcement. 21 (75%) of our patients had documented prior wound or deep organ space infections such as gangrenous cholecystitis, perforated diverticulitis or infected pancreatic necrosis. 6 patients had multiple failed hernia repairs with mesh implantation, prior GI surgery, or ostomy take down at the time of our index hernia repair. One had cirrhosis with severe portal hypertension. According to the CDC wound classification, 20 of our patients had a class I wound at the time of our hernia repair. However, 19 of this class I patients had prior wound or deep organ space infections as described. Only our cirrhotic patient did not have any infections, hernia repairs or ostomies prior to the index hernia surgery.

We have evaluated postoperative outcomes during short and mid-term follow ups, the longest being 42 months. During follow-ups, we had no hernia recurrence. Only one of our 5 only hernia repairs was complicated with seroma formation, and we encountered two infected hematoma cases, with hematoma formation over the mesh, posterior to the recti muscles. Fortunately, both of these hematomas were resolved with no mesh or hernia repair compromise as documented in Fig 2. We did not have to explant mesh in any of our complication.

This study has its inherent limitations. It represents our very limited experience, and the low sample size cannot justify extrapolation of the data for change of clinical practice. Furthermore, it is a retrospective data analysis of a prospectively maintained hernia database without a control arm. In order to mitigate this deficiency, we have used the ACS NSQIP surgical risk calculator as our virtual matched control and comparison benchmark. The information for each patient was entered into this online risk calculator, and the predicted outcomes were obtained as seen in Table 4. It indicates that our complication rates and wound events were higher than expected (39% actual vs. 18% expected), with lower readmission (4% actual vs 11% expected) and a comparable reoperation rate (7% actual vs. 6% expected). Despite having a higher complication rate than the predicted outcome, our length of stay was around the predicted value (6 days actual vs. 5 days expected).

To date, we could not find any reports in the literature describing the mid-term histologic properties of P4HB in human tissue and associated host response after hernia repair with P4HB mesh implantation. We had a unique opportunity to perform a full-thickness abdominal wall biopsy from a very complex patient, 14 months after abdominal wall reconstruction with P4HB and bilateral posterior component separations. Our patient is a 56-year-old male who had sustained over 65% body surface area burns, resulting in a prolonged hospital stay, at least five abdominal surgeries which were complicated with wound and fascial dehiscence, multiple multi-microbial wound and deep organ space infections, and skin grafts resulting in a large ventral incisional hernia. The patient presented again with acute cholecystitis, 14 months after his index abdominal wall reconstruction as described above, which was managed by laparoscopic cholecystectomy. Full-thickness abdominal wall biopsy was taken at the time of port placement in the right upper quadrant. H&E, Trichrome and CD68 immunostains were performed.

Our histologic evaluation reveals that mesh was still present in the tissue 14 months post-implantation. It confirms a dense collagen scaffold formation around the mesh with small aggregates of pro-inflammatory cells. This finding is suggestive of low inflammatory response to the P4HB in human abdominal wall tissue with no acute inflammation or granuloma formation during mid-term follow up. These findings are similar to Scott et al. and Deeken et al. reports of P4HB histologic behavior in a porcine abdominal wall model [21, 12].

Our limited experience shows that P4HB can be successfully used in high risk clean, clean-contaminated and contaminated cases with no postoperative mesh explanation or hernia recurrences, despite serious complications such as infected hematomas. Furthermore, pathologic evaluation of the human tissue 14 months after successful implantation of mesh confirms mesh presence with surrounding dense collagen scaffold formation and minimal inflammatory response.

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Dr. Fathi and Dr. Bilello were the operating surgeons for the cases in this study. Dr. Slater provided a histo-pathological analysis of the specimens. Dr. Ladella compiled the data and wrote the manuscript. Dr. Pooya compiled and sorted the references for the final manuscript.

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