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Bacterial clearance of biologic grafts used in hernia repair: an experimental study

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Abstract

Background—Biologic grafts used in ventral hernia repair are derived from various sources and undergo different post-tissue-harvesting processing, handling, and sterilization techniques. It is unclear how these various characteristics impact graft response in the setting of contamination. We evaluated four materials in an infected hernia repair animal model using fluorescence imaging and quantitative culture studies.

Methods—One hundred seven rats underwent creation of a chronic hernia. They were then repaired with one synthetic polyester control material ($n = 12$) and four different biologic grafts ($n = 24$ per material). Biologic grafts evaluated included Surgisis (porcine small intestinal submucosa), Permacol (crosslinked porcine dermis), Xenmatrix (noncrosslinked porcine dermis), and Strattice (noncrosslinked porcine dermis). Half of the repairs in each group were inoculated

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with *Staphylococcus aureus* at 10^4 CFU/ml and survived for 30 days without systemic antibiotics. Animals then underwent fluorescence imaging and quantitative bacterial studies.

Results—All clean repairs remained sterile. Rates of bacterial clearance were as follows: polyester synthetic 0%, Surgisis 58%, Permacol 67%, Xenmatrix 75%, and Strattice 92% ($P = 0.003$). Quantitative bacterial counts had a similar trend in bacterial clearance: polyester synthetic 1×10^6 CFU/g, Surgisis 4.3×10^5 CFU/g, Permacol 1.7×10^3 CFU/g, Xenmatrix 46 CFU/g, and Strattice 31 CFU/g ($P = 0.001$). Fluorescence imaging was unable to detect low bacterial fluorescence counts observed on bacterial studies.

Conclusion—Biologic grafts, in comparison to synthetic material, are able to clear a *Staphylococcus aureus* contamination; however, they are able to do so at different rates. Bacterial clearance correlated to the level of residual bacterial burden observed in our study. Post-tissue-harvesting processing, handling, and sterilization techniques may contribute to this observed difference in ability to clear bacteria.

Keywords

Biologic mesh; Infection; Hernia repair

The repair of complex hernias in the setting of infection is a challenging problem that has traditionally been approached with staged repair. The introduction of biologic grafts into surgical practice over the last decade has provided surgeons with a potentially more favorable alternative in the setting of contamination where synthetic materials are otherwise contraindicated.

To date, there are at least 12 biologic grafts approved for the repair of ventral abdominal wall defects. Despite the general term “biologic grafts,” their characteristics are heterogeneous and they are derived from various sources (porcine dermis, bovine dermis, bovine pericardium, porcine small intestinal submucosa, human dermis, and fetal bovine dermis), undergo different tissue processing (no crosslinking, diisocyanate crosslinking, glutaraldehyde crosslinking, or EDAC crosslinking), and different sterilization techniques (ethylene oxide, gamma radiation, liquid alcohol, e-beam radiation) [1].

It is unclear how these various characteristics might impact the graft’s response in the setting of contamination. The availability of clinical studies in the setting of infection for many of these materials is limited, with no single clinical study comparing outcomes associated with two or more materials when exposed to the same infectious challenge. Through the use of fluorescence imaging and quantitative culture studies, we compare four biologic grafts and their ability to clear a *Staphylococcus aureus* contamination compared to a synthetic mesh in a chronic hernia repair animal model.

Materials and methods

Animals

Female Sprague-Dawley rats (Charles River Inc., Wilmington, MA), weighing between 200 and 220 g, were acclimated and housed under standard conditions. All animal care and operative procedures were performed in accordance with the U.S. Public Health Service Guide for the Care of Laboratory Animals (NIH Publication 85–23, 1985) and were performed with the prior approval of the Case University Institutional Animal Care and Use Committee. Animals were allowed ad libitum intake of standard rat chow and water throughout the study. Prior to both surgeries, animals underwent general anesthesia with inhaled isoflurane, and the abdominal wall was clipped and prepped with 70% chlorhexidine. Following every surgery, pain control consisted of local marcaine (5%

diluted 1:10) at the time of incision closure and subcutaneous buprenorphine (0.03 mg/100 g) daily for four days. No systemically administered antibiotics were given during this study.

Hernia induction

One hundred seven rats underwent creation of a chronic hernia. A 1-cm transverse incision was made at the level of the xiphoid. A full-thickness skin flap (5 cm) was created at the avascular prefascial plane above the linea alba. The linea alba was then sharply cut under direct visualization for 4 cm to create a full-thickness laparotomy. The skin was then closed 4-0 Vicryl. After surviving 30 days, rats developed an abdominal wall hernia.

Chronic hernia repair

Animals were randomly assigned to undergo biologic mesh bridge repair (0.5-cm mesh-tissue overlap) with Permacol (Covidien, Mansfield, MA) (crosslinked porcine dermis; $n = 24$), Surgisis (Cook, Bloomington, IN) (noncrosslinked porcine small intestinal submucosa; $n = 24$), Xenmatrix (Bard Davol, Warwick, RI) (noncrosslinked porcine dermis; $n = 24$), or Stratattice (LifeCell, Branchburg, NJ) (noncrosslinked porcine dermis; $n = 24$). Prior to implantation, all materials were properly rehydrated or soaked as directed by the manufacturer. Another group of animals were randomized to the synthetic control arm in which Parietex (Covidien) (three-dimensional polyester woven mesh; $n = 12$) was used. A full-thickness skin flap was created in the prefascial avascular plane beginning at the prior xiphoid incision and extended caudally to create a flap beginning 1 cm lateral to the midline. Following hernia sac excision, the hernia defect was measured and the mesh was then secured in place with interrupted 4-0 Prolene sutures approximately 0.5 cm apart. Following skin closure, half the animals in each group were inoculated as described below and survived for 30 days. The remaining animals underwent sterile closure to serve as the uninfected clean controls.

Bacterial preparation and infecting hernia repairs

A clinical strain (Seattle 1945) of *Staphylococcus aureus* (SA) transformed with a green fluorescent protein (GFP)-labeled plasmid to produce SA 1945GFP_{uvr} was used in this study [2]. The strain was recovered from storage at -70°C by subculture onto a tryptic soy agar (TSA) plate with 5% sheep blood, which was then incubated at 37°C for 24 h. An individual colony was then inoculated in 5 ml of brain heart infusion (BHI) broth and incubated in a 37°C shaker at 200 rpm for 24 h. A 1:50 dilution of the overnight bacterial broth was then created and placed in a 37°C shaker at 200 rpm for 2.5 h, allowing the bacteria to reach log phase growth at a concentration of 10^8 CFU/ml based on optical density. This growth was then serially diluted in sterile 0.9% normal saline (NS) to a concentration of 10^5 CFU/ml and a 100- μl volume was used as the inoculum for the infected animals. Half the animals in each group were inoculated with GFP SA (contaminated cases, $n = 12$ per biologic group; $n = 6$ per synthetic mesh). The inoculum was introduced onto each mesh following skin closure via a skin puncture with a 25-gauge needle. The viability and inoculum concentration of the culture were verified on the day of the study. For our in vitro Maestro imaging studies, the same methodology was used and serial dilutions (10^3 – 10^8 CFU/ml) of GFP SA broth were created.

Necropsy and culture studies

Animals were euthanized 30 days after hernia repair and the abdominal wall was clipped and prepped with chlorhexidine. After the skin was sharply removed from the abdominal wall, a full-thickness abdominal wall explant was procured. Abdominal wall explants underwent immediate fluorescence imaging using Maestro (methods described below). Following imaging, a 6-mm sterile punch biopsy of both tissue and mesh was obtained,

weighed, placed in 1 cc of sterile 0.9% saline, and homogenized. Serial tenfold dilutions of the mesh and tissue homogenate were made in 0.9% saline and 100- μ l volumes of the original suspension, then the dilutions were plated on TSA plates with 5% sheep blood and incubated for 48 h at 37°C. Bacterial growth was quantified from plates showing 30–300 CFU per plate and expressed as CFU/g of specimen based on the weight of each specimen. Bacterial clearance, as a percentage, was defined as the number of animals with sterile cultures divided by the total number of infected animals. GFP SA was identified on plates by green fluorescence emitted from colonies after UV light exposure. Colonies that did not fluoresce were identified by conventional microbiological methods.

Maestro fluorescence imaging

Spectral fluorescence images of serial bacterial broth concentrations and explanted abdominal wall were obtained using the Maestro™ In-Vivo Imaging System (CRi, Inc., Woburn, MA). A bandpass filter appropriate for the fluorochrome of interest (GFP; $E_x = 445\text{--}490$ nm, $E_m = 515$ long pass filter; acquisition settings = 500–720) was used for excitation and emission light, respectively. The tunable filter was automatically stepped in 10-nm increments while the camera captured images at an autoexposure. To evaluate signal intensities, regions of interest (ROI) were selected over the subject of interest and the total fluorescence signal was determined. Total signal in the ROI (in photons) measured at the surface of the subject of interest is divided by its area (in pixels) as well as exposure time (in ms). The spectral fluorescent images consisting of autofluorescence spectra and GFP SA were captured and unmixed based on their spectral patterns using Maestro™ software (CRi, Inc.). Spectral libraries were generated by assigning spectral peaks to background autofluorescence (biologic mesh and tissue), background from the imaging stage and in vitro plate, and fluorescence from GFP bacteria. The spectral libraries were manually computed using the Maestro software. All analysis was based on the spectral library determined from the spectral shift. Maestro signal intensities are represented as relative fluorescence units (RFUs).

In vitro imaging—Using a 24-black-well plate, Maestro imaging was performed on serial concentrations ($10^3\text{--}10^8$ CFU/ml) of GFP SA in 1-cc volumes as described above. This method allowed us to determine the minimal level of GFP SA signal detection using Maestro imaging.

Abdominal wall explants imaging—The same Maestro settings were then used when imaging the explanted abdominal walls. In order to subtract any background autofluorescence derived from the biologic material, abdominal wall explants of control (clean) repairs were used as the imaging control. Half the animals in the biologic graft group were imaged ($n = 12$ per material; total $n = 48$), while all the synthetic abdominal wall explants were imaged ($n = 12$).

Data analysis

Data were analyzed using Stata 10 (StataCorp LP, College Station, TX). A correlation curve was determined for the in vitro study. Percent bacterial clearance and average bacterial counts (in CFU/g) were obtained following culture studies. For statistical purposes, when no GFP SA was detected on TSA plates, the minimum number of colonies detectable was used (300 CFU/ml) in place of a 0-CFU/ml count. Culture results were otherwise reported based on obtained bacterial growth numbers. Mann-Whitney, post-hoc, and Fisher's exact tests were performed where appropriate, and $P < 0.05$ was considered significant.

Results

One hundred seven animals underwent hernia repair and 106 survived 30 days following repair. One early technical related death occurred in a sterile repair group (Strattice). Low numbers of coagulase negative and positive staphylococci (not the GFP SA inoculated) were isolated from a few samples, likely derived from skin contamination at the time of surgical necropsy and were excluded from analysis.

Microbiology results

Clean cases—All clean repair cultures (Permacol, Surgisis, Xenmatrix, Strattice, and Parietex) remained sterile after a 30-day survival.

Contaminated cases—None of the infected synthetic Parietex repairs cleared the GFP SA infection (0%; $n = 0/6$). A decreased and varied rate of bacterial clearance was observed across the four biologic grafts: Surgisis 58% ($n = 7/12$), Permacol 67% ($n = 8/12$), Xenmatrix 75% ($n = 9/12$), and Strattice 92% ($n = 11/12$) (Fig. 1). There was a statistically significant difference in rates of GFP SA bacterial clearance across all five infected groups ($P = 0.003$). Quantitative bacterial counts for GFP SA showed a similar trend for bacterial clearance: Parietex 1×10^6 CFU/g ($SD = 6.7 \times 10^5$ CFU/g), Surgisis 4.3×10^5 CFU/g ($SD = 1.4 \times 10^6$ CFU/g), Permacol 1.7×10^3 CFU/g ($SD = 4.3 \times 10^3$ CFU/g), Xenmatrix 46 CFU/g ($SD = 88$ CFU/g), and Strattice 31 CFU/g ($SD = 1 \times 10^2$ CFU/g) ($P = 0.001$). When the bacterial counts of the four biologic grafts were compared alone, there was a significant difference among them as well ($P = 0.01$).

In vitro Maestro imaging

There was a positive linear correlation ($R^2 = 0.9121$; $Y = 715X + 186$) between the Maestro fluorescence imaging signal and bacterial counts in GFP SA broth serial dilutions above a concentration of 10^5 CFU/ml. Below this concentration, Maestro fluorescence imaging was unable to detect an adequate GFP signal. This was determined to be the lower limit of GFP SA detection with Maestro fluorescence imaging.

Explant Maestro imaging

At baseline, all biologic materials had a high inherent green autofluorescence, which fell into a range similar to that of the GFP fluorescence spectra. Imaging of abdominal wall explants was unable to detect the presence of GFP SA in the contaminated animals or a difference in fluorescence signal between clean and contaminated cases (0 RFU signal/group). While quantitative microbiology studies more accurately represented GFP SA growth in some specimens, the persistent bacterial burden appeared to be below the detectable limit of Maestro fluorescence imaging. The discussion that follows is based primarily on our quantitative microbiology results.

Discussion

Use of the widely available biologic grafts in the setting of contaminated abdominal wall reconstruction is increasing despite a lack of extensive evaluation of their ability to clear bacteria under contaminated conditions. To our knowledge, this is the first animal study that compares four biologic grafts with the same bacterial contamination methodology. Using quantitative bacterial culture studies, we showed that biologic grafts, compared to a synthetic material, can decrease or clear a *Staphylococcus aureus* (SA) contamination in the setting of a chronic hernia repair model, with varied ability noted across the different materials.

Considering the quantity and variety of biologic grafts available to the reconstructive surgeon, there is a lack of studies evaluating these materials in a preclinical setting. Of the available studies in the literature, most are limited to three materials: Permacol, Surgisis, and Alloderm [3–19]. While these studies evaluate important characteristics associated with biologic grafts, they do so in a sterile setting. Such studies serve as measures of safety and possible outcomes under the most ideal circumstances. These studies are often difficult to translate into current clinical practice because most biologic grafts will be placed in a contaminated setting, where synthetic meshes are otherwise contraindicated. While there are a few studies in which biologic materials are exposed to a bacterial challenge, a short survival time and varied bacterial techniques limit interpretation [20–22].

In our study we exposed four biologic grafts to a moderate level of bacterial inoculum with SA at the time of repair (10^4 CFU/ml GFP SA) and evaluated them at 30 days with quantitative cultures (CFU/g) and fluorescence imaging. When compared to our synthetic infection control group, all biologic materials appeared to clear the contamination more effectively, with 50% or less of them actually growing any SA on quantitative bacterial cultures. In addition, the biologic grafts had decreased bacterial burden (CFU/g) compared to the synthetic control mesh. Maestro fluorescence imaging was unable to detect the presence of GFP SA across our materials primarily because of the overall low bacterial burden present on the biologic grafts. The ability to clear contamination, however, was quite varied among the different materials as evidenced by our quantitative microbiology results.

The biologic grafts compared in our study are widely available materials that are inherently different based on source and post-tissue-harvesting processing techniques. Their inherent differences might play an important role in how well they can clear SA contamination. While all materials in our study are porcine-derived, three are from dermal sources (Permacol, Xenmatrix, and Strattice), one has small intestinal submucosa as its source (Surgisis), and one undergoes the chemical processing of crosslinking (Permacol). Surgisis had the highest overall bacterial recovery on quantitative cultures, an outcome that might have been related to the delamination process and the subsequent central region of poor tissue infiltration found in our animals on gross inspection. In our study we had available the 8-ply design of Surgisis. It would be interesting to evaluate and compare our current findings to those of the more recent Surgisis designs as their modification in processing techniques might change our results.

In comparison to Surgisis, the dermal-based products (Permacol, Xenmatrix, and Strattice) all appeared intact with no gross material breakdown noted on necropsy. This lack of breakdown might have provided a more favorable scenario for the host to address the infection. Despite appearing grossly unchanged, Permacol had the second highest bacterial burden on quantitative cultures. This may be a characteristic that could be related to its crosslinking processing. While the process of crosslinking is intended to prevent host and bacterial collagenase-induced degradation, there is also concern that crosslinking may prevent fibroblast infiltration and adequate native tissue ingrowth [1, 23, 24]. This may have impeded the ability of the host to decrease the bacterial burden. Indeed, prior histopathology-based animal studies have noted decreased tissue ingrowth with this material [6, 8]. The last two materials, Xenmatrix and Strattice, two noncrosslinked dermal-based biologics, had the least persistent bacterial burden on 30-day quantitative cultures. In addition to these characteristics, these two materials are both e-beam sterilized which is a different processing technique compared to Permacol (γ irradiation sterilized) and Surgisis (EO sterilized). There may certainly be other processing techniques that influence how these materials are able to clear bacteria, but this information is largely proprietary, thus limiting their evaluation.

In our study we chose to evaluate persistent bacterial burden by using both quantitative bacterial cultures and quantitative fluorescence Maestro imaging. Our quantitative approach was important as it provided “tissue-level” bacterial burden. The importance of showing bacterial burden as a measure of the ability to close a wound successfully was shown in the classic work by Krizek et al. [25]. Their work in quantitative bacteriology attempted to predict successful closure of a wound in the face of bacterial contamination. Through their work, a bacterial burden of 10^5 CFU/g or less predicted the successful closure of a contaminated wound. Similar studies in allograft burn and wound coverage have shown successful “take” of the grafts when placed in the setting of 10^5 CFU/g or less [25, 26]. Such a reference (10^5 CFU/g) may have potential relevance and importance in how we evaluate currently used biologic grafts in the setting of contaminated abdominal wall reconstruction.

Maestro imaging in our model was certainly limited by a detection threshold and possibly the location and depth of the fluorescence. The chosen inoculum for this study (10^4 CFU/ml) started off below the detectable limit for Maestro fluorescence imaging. Given the overall low GFP SA bacterial counts among our biologics, it is apparent that the organism did not proliferate to its potential. One of the drawbacks of Maestro imaging is that it is unable to accurately detect fluorescence that is deeply embedded in tissue. For the field of biologic grafts, Maestro fluorescence imaging using green fluorescence certainly has its limitations. Several innovative alternatives can be considered in order to overcome the challenges associated with abdominal wall explant or in vivo imaging. The use of red fluorescent-tagged bacteria or luciferase-tagged bacteria could allow for in vivo bacterial detection [27]. Despite this imaging limitation, we were still able to detect the bacteria’s green fluorescence under UV light during our quantitative bacterial cultures, thus allowing us to accurately compare the varied responses across materials to this setting of contamination.

Longer serial evaluations of these biomaterials are important in understanding the materials’ ability to provide a durable hernia repair in the setting of contamination. This is a critical question in light of their apparent differences in their ability to clear infection. It would be important to translate these studies to include other bacterial agents involved in abdominal wall repair infections as well. MRSA, for example, is an important pathogen in mesh infections containing different virulence factors compared to MSSA, which may change the ability of these materials to clear infection. Furthermore, histology and biomechanics would be important in understanding their true potential for allowing neovascularization and fibroblast ingrowth with eventual native tissue replacement leading to a strong repair.

Biologic grafts can better clear a SA contamination than a synthetic material. However, the ability to do so varied across the different materials evaluated in our study. This may have been secondary to their differences in tissue source, processing, and sterilization techniques. Further studies evaluating the potential of these materials to serve as a long-term durable hernia repair in the setting of infection are needed.

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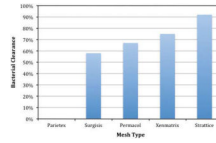


Fig. 1. Rates of *Staphylococcus aureus* bacterial clearance achieved among various hernia repair materials after a 30-day survival in an infected hernia repair rat model ($P = 0.003$)