Biomaterials: So Many Choices, So Little Time. What Are the Differences?

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Abstract

The use of biologic mesh has increased greatly in recent years in response to the need for a solution in managing contaminated hernias. Multiple different meshes are commercially available, and are derived from a variety of sources, including human dermis as well as animal sources. For a mesh to be effective, it must be resistant to infection, have adequate tensile strength for hernia repair, and be well tolerated by the host. To achieve this end, biologic meshes go through an intense processing that varies from one product to the next. In this article, the authors review the types of mesh available, how they are processed, and examine these characteristics in terms of their strengths and weaknesses in application to surgical technique.

Keywords

- biologic mesh
- cross-linking
- xenograft
- ventral hernia

CME Objectives: Upon completion of this article, the reader should be able to summarize the various sources used for biologic mesh and the goals of mesh processing.

The use of biologic mesh has increased dramatically in the past 10 years. In the field of abdominal wall reconstruction, biologic mesh has offered solutions to some of the difficult problems with synthetic mesh repair. Synthetic mesh repair can be complicated by chronic inflammation, enteric erosion, contraction, pain, loss of compliance, and bacterial colonization. The theory behind biologics is to provide a graft material that not only affords strength toward the surgical repair but also integrates over time into the host tissue by way of angiogenesis, cellular infiltration, and collagen deposition.¹ These attributes allow its use in contaminated fields with less fear of mesh infection. In this section, we will look at some of the characteristics of biologic meshes and their manufacturing techniques in an effort to gain a better understanding of their strengths and weaknesses in application to surgical technique. ► **Table 1** provides a summary of various biologic meshes and selected characteristics.

Xenografts versus Homografts

Biologic meshes are available as xenografts (porcine or bovine) or homografts (human cadaver). Biologic meshes are heavily

processed to decellularize, sterilize, and strengthen the product. These various processing techniques employed by mesh manufacturers are proprietary and thus differ widely between products. It is believed that the processing technique, and not the tissue of origin, is the basis for the induced tissue reaction of the host.²

Both the innate and acquired host immune system will respond to foreign cellular protein and can lead to a reaction anywhere from mild inflammation to acute rejection. Components of the extracellular matrix (ECM) are generally conserved among species and thus well tolerated.³ A key component to biologic mesh manufacturing is the decellularization process, whereby the donor tissue's cells are removed leaving behind a collagen matrix scaffold. It has been shown that the greater the amount of cellular debris left behind in the matrix scaffold, the greater the host inflammatory response and adverse remodeling response will be.⁴ The decellularization process varies between products. Decellularization can include processing the tissue with hyper- or hypotonic solutions, acids and bases, detergents, organic solvents, alcohol solvents, proteases, nucleases, chelating agents, and toxins.⁵ Subjecting the tissue to physical forces through freezing and thawing, direct pressure, electroporation, and perfusion are also potential components of the decellularization process. It is impossible to remove all cellular debris, as some will be well incorporated within the acellular collagen matrix.⁶ A delicate balance exists between

Table 1 Types and characteristics of biologic meshes

Product name	Manufacturer	Source	Cross-linked	Decellularization/ Sterilization process	Size/Thickness	Rehydration required	Refrigeration required	Tear resistance ^{ab}	Strain at 16 N/cm (%) ^{ac}	Suture retention strength ^{ab}
Alloderm	LifeCell (Bridgewater, NJ)	Human dermis	No	Ionic detergent (sodium deoxycholate) Aseptic proprietary processing, freeze-dried	1 × 1–16 × 20 cm 0.23–3.30 mm	Yes	No	> 20 N	10–30%	> 20 N
AlloMax	Bard/Davol (Murray Hill, NJ)	Human dermis	No	Organic and aqueous solvents γ-irradiation	2 × 4–16 × 20 cm 0.8–1 mm	Yes	No	≤ 20 N	10–30%	> 20 N
FlexHD	Ethicon/MTF (Somerville, NJ)	Human dermis	No	Ionic Aseptic processing	1 × 2–12 × 24 cm 0.4–1.8+ mm	No	No	> 20 N	10–30%	> 20 N
DermaMatrix	Synthes/MTF (West Chester, PA)	Human dermis	No	Ionic detergent Aseptic proprietary processing, freeze-dried	1 × 2–20 × 25 cm 0.2–1.8+ mm	Yes	No	–	–	–
XenMatrix	Bard/Davol (Murray Hill, NJ)	Porcine dermis	No	Ionic detergent, hyper/hypotonic saline Electron beam irradiation	10 × 15–19 × 35 cm –	No	No	> 20 N	10–30%	> 20 N
Strattice	LifeCell (Bridgewater, NJ)	Porcine dermis	No	Proprietary process Electron beam irradiation	6 × 6–25 × 40 cm –	Yes	No	> 20 N	≤ 10%	> 20 N
XCM	Synthes (West Chester, PA)	Porcine dermis	No	Proprietary Optrix process Terminally sterilized	2 × 2–20 × 30 cm –	No	No	–	–	–
Permacol	Covidien (Mansfield, MA)	Porcine dermis	HMDI	Enzymatic γ – Irradiation	1 × 4–28 × 40 cm 0.5–1.5 cm	No	No	≤ 20 N	10–30%	> 20 N
Surgimend	TEI Biosciences (Waltham, MA)	Bovine dermis	No	Proprietary process Ethylene oxide gas	0.3 × 25–25 × 40 cm 1–4 mm	Yes	No	> 20 N	≤ 10%	> 20 N
Tutopatch	RTI Surgical (Alachua, FL)	Bovine pericardium	No	Organic and aqueous solvents γ-irradiation	4 × 5–12 × 16 cm –	Yes	No	–	–	–

(Continued)

Table 1 (Continued)

Product name	Manufacturer	Source	Cross-linked	Decellularization/ Sterilization process	Size/Thickness	Rehydration required	Refrigeration required	Tear resistance ^{ab}	Strain at 16 N/cm (%) ^{ac}	Suture retention strength ^{ab}
Periguard	Synovis (Deerfield, IL)	Bovine pericardium	Glutaraldehyde	Proprietary Apex processing—sodium hydroxide Ethanol, propylene oxide	4 × 4–12 × 25 cm –	Yes	No	≤ 20 N	10–30%	> 20 N
Veritas	Synovis (Deerfield, IL)	Bovine pericardium	No	Proprietary Veritas processing—sodium hydroxide, propylene oxide, ethanol Electron beam irradiation	2 × 8–12 × 25 cm –	No	No	≤ 20 N	10–30%	> 20 N
Biodesign (formerly Surgisis)	Cook (Bloomington, IN)	Porcine intestine	No	Peracetic acid Ethylene oxide	4 × 7–20 × 30 cm –	Yes	No	> 20 N	10–30%	> 20 N

Abbreviation: HMDI, hexamethylene diisocyanate.

^aBased on data from Deeken C, Eliason B. Differentiation of biologic scaffold materials through physicochemical, thermal, and enzymatic degradation techniques. *Ann Surg* 2012;255(3):595–604.^b> 20 N accepted threshold for hernia repair.^c10 to 30% tissue strain when subjected to 16 N/cm of force is the accepted threshold for hernia repair.

removing as much cellular debris as possible and preserving the acellular matrix scaffold. This is where proprietary processes come into play and characteristic variation can develop among the products. Standards exist to define the maximum amount of cellular debris allowable in these products and the majority fall well within these guidelines.⁷

The use of xenograft material presents an obvious concern for host rejection. α -Galactosyl (α Gal) is a cellular epitope expressed by pigs and other nonprimate mammals.⁸ Humans express large quantities of anti- α Gal antibodies due to stimulation from intestinal flora that contain the antigen. Thus, this epitope is one of the major causes of rejection in whole organ xenotransplantation. The decellularization process works to rid the tissue of cellular α Gal, but non-cell-associated α Gal can remain behind integrated into the acellular collagen matrix. In 2000, McPherson et al proved the persistence of small quantities of α Gal after decellularization. They also showed minimal host inflammatory response, hypothesizing that the quantity of α Gal was inefficient to activate complement.⁹ Further studies by Daly et al on porcine-derived xenograft confirmed the presence of α Gal, documented a diminished host immune response, and further showed no adverse effect on tissue remodeling when compared with an allograft.¹⁰

Evidence has strongly shown that the decellularization processes effectively rids the xenograft tissue of clinically relevant quantities of cellular material and truncates the host immune response to a level that prevents rejection and adverse graft remodeling. These data along with the successful transplant of millions of xenografts to date support their safe and efficacious use as biologic meshes.⁵

Dermis versus Nondermis

Whether xenogeneic or allogeneic, the anatomic source of the graft tissue can vary from product to product as well. The major biologic grafts available today are sourced from dermis, pericardium, intestine, and bladder. These tissues are rich in collagen and thus provide the strong scaffolding matrix needed for surgery. Human dermis was the dominant source when biologic mesh was first introduced. However, increased human tissue banking regulations, difficulty with screening human tissue for infectious disease, and limited supply led to the advent of xenograft as biologic material. These tissues are less expensive to obtain and more readily available. They are regulated by the Food and Drug Administration (FDA) as opposed to tissue banks, which allows for better processing quality control by the mesh manufacturer.¹¹ With the advent of xenografts came the option to use other tissue sources such as intestine and pericardium.

Dermis is the most common source as it can be produced in larger sizes desired in hernia repair, and is available in a 28 × 40 cm size. Its thickness provides a strong scaffold for abdominal wall repairs. However, it contains a high amount of elastin and has been shown to stretch over time.

In the late 1990s, porcine small intestine submucosal derived mesh was introduced. The material is thinner than dermal-derived mesh but when laminated in 4- and 8-ply configurations, it provides significant strength for body-wall

deficit repairs. There is minimal elastin present, so it is less susceptible to stretch over time. The main advantage touted for intestine-derived graft is its ability to rapidly incorporate and degrade while leaving the host tissue stronger than before.¹² Neovascularization occurs rapidly, possibly leading to increased collagen remodeling, graft degradation, and increased infection resistance.¹³

Pericardium has become another popular tissue source for grafts. It is pliable and generally easy to work with. It has naturally multidirectional collagen fibers, leading to a strong scaffold. It is low in cellularity and thus the decellularization process is simpler. It also contains minimal elastin, making it less susceptible to stretch over time.¹⁴

Cross-linking

The deterioration of donor tissue begins to occur as soon as the tissue is harvested. This process is accelerated once implanted, where the host collagenases begin to break down the graft. To combat this effect, chemical cross-linking is used to stabilize the collagen matrix and protect the graft from degradation both on the shelf and in the host. Chemicals used include glutaraldehyde, polyether oxide, hexamethylene diisocyanate, acyl azide, and glycerol. These chemicals are toxic and must be thoroughly washed out once the graft is treated. However, concern remains for chemicals that remain trapped within the matrix and their effect on the host. Although graft strength is important at the time of operation and in the earlier phases of recovery, at some point host tissue integration must occur and breakdown of the donor graft should commence. Thus, there is a delicate balance with the cross-linking process to provide initial strength but not hinder the integration process.¹⁵

Leather is an example of maximally cross-linked dermis. So, it follows that overly cross-linked biologic mesh would tend to not integrate and ultimately become encapsulated and treated as a foreign body. Animal studies comparing cross-linked and non-cross-linked grafts at 1, 2, and 4 weeks after implantation have shown better host cell and vessel integration, less adhesion to underlying bowel, less postoperative wound complications, and stronger bioprosthetic-musculofascial bonds in the non-cross-linked mesh.¹⁶ The encapsulation and poor integration of cross-linked grafts may only be a short-term effect, however, as histologic analysis at 6 to 12 months has shown equivalency with non-cross-linked graft integration.¹⁷

Processing

The goal of processing donor tissue for use as an implantable graft is to rid the tissue of all cellular products while maintaining the complex composition and three-dimensional ultrastructure of the ECM. The ECM ultrastructure, surface topology, and composition influence host cell migration and differentiation, and thus the overall tissue remodeling response. Tissue processing and decellularization are critical to the success of a biologic graft. The combination of physical, chemical, and biologic processing methods is a proprietary process unique to each manufacturer. Within these

companies, careful decisions are made regarding which techniques to employ to optimize tissue decellularization while maintaining ECM structural integrity and bioactivity.

Gilbert et al describe a general decellularization protocol combining physical, chemical, and enzymatic processes. It begins with lysis of the cell membrane using physical or ionic treatments. This is typically followed by separation of cellular components from the ECM with enzymatic treatments, then solubilization of cytoplasmic and nuclear components with detergents, and finally removal of cellular debris. Mechanical forces such as agitation and pressure gradients can be added to enhance the process.³ The effectiveness of each of these methods is dependent on the host tissue itself, including the cellularity, density, lipid content, and thickness.⁶ What follows is a brief overview of chemical, biologic, and physical decellularization agents, based on an overview of the processes by Crapo et al updated in 2011.

Chemical agents include acids and bases, hypo- and hypertonic solutions, detergents, alcohols, and other solvents. Acids and bases cause hydrolytic degradation leading to solubilization of cytoplasmic components, disruption of nucleic acids, and protein denaturing. Peracetic acid is commonly used, as it is effective at decellularization and disinfection while minimally affecting the ECM structure. Bases are effective at dermal hair removal early in the process, but can eliminate growth factors from and reduce the mechanical properties of the ECM. Hyper- and hypotonic solutions cause effective cell lysis by simple osmotic effect as well as disrupting DNA-protein interactions. They have minimal impact on the structure and biologic function of the ECM. They are commonly employed together in alternating hyper- and hypotonic baths for maximal effect, but do not effectively remove cellular residues. Detergents (ionic, nonionic, and zwitterionic) solubilize cell membranes and dissociate DNA-protein bonds. They exhibit variable disruption of the ECM structure, growth factor removal, and direct collagen damage. Detergents must be completely flushed from the tissue before use, as they are cytotoxic and small amounts can cause inflammation and prevent graft incorporation. Alcohols work by dehydrating and lysing cells. They can, however, have the unintended effect of cross-linking proteins and collagen.

Biologic agents are either enzymatic or nonenzymatic. Enzymes used in decellularization include nucleases, trypsin, collagenase, lipase, dispase, thermolysin, and α -galactosidase. Enzymes are highly specific and effective at removing cellular components. The residues left behind can cause unwanted immune response and ECM structure damage. Nonenzymatic biologic agents include chelating agents that bind metallic ions and disrupt cell adhesion to the ECM. They are typically used in combination with enzymatic agents.

Physical agents include temperature, force, and pressure. Multiple freeze-thaw cycles have been shown to effectively lyse cells with minor disruption of the ECM structure. Mechanical abrasion can be used in combination with enzymes, hypertonic saline, and chelating agents to remove cells from an underlying membrane. However, the mechanical force can compromise the integrity of the basement membrane.

A final and very important component to tissue processing is sterilization. Simple incubation in acids or solvents can be effective for thin or porous ECMs, but can cause specific damage to ECMs and may have poor penetration in thicker tissues. Other popular sterilization methods include ethylene oxide exposure, gamma irradiation, and electron beam irradiation. However, ethylene oxide has been shown to substantially change ECM mechanical properties in some instances, as well as invoke unwanted immune response in the host. Irradiation techniques can cause residual lipid to become cytotoxic and accelerate host enzymatic degradation of the ECM.⁶

Resistance to Infection

One of the main marketed advantages of biologic mesh is its ability to be used in a contaminated field without the fear of infection and need for explantation. In theory, the vascular ingrowth that occurs with biologics allows the host immune system to fight infection, as opposed to synthetic meshes where no ingrowth occurs. However, biologics can still be affected by bacterial contamination. Many bacteria produce collagenase that can directly affect the structural integrity of the ECM, especially in non-cross-linked products. Rat models have shown that the degree of contamination will affect the bacterial clearance rate, wound complication rate, and strength of repair.¹⁸ Other animal studies have shown poor cellular and revascularization of both human dermis and porcine intestinal meshes when infected with *Pseudomonas*. Interestingly, the biomechanical properties of the porcine intestinal mesh were much more negatively affected than those of the human dermis.¹⁹

Biologics have set the stage for single-staged contaminated hernia repairs. A single-stage approach allows avoidance of a multistaged process that often involves temporary abdominal closures and prolonged hospital and recovery times, sometimes on the order of 6 to 12 months. Retrospective and single-institution studies have shown successful single-staged hernia repairs with biologic mesh in a population of contaminated reconstruction patients, avoiding complete excisions, draining sinuses, and mesh infections. However, wound complication rates were upward of 30%. And while short-term recurrence rates were only 11 to 12%, 3-year recurrence rates reached as high as 50%.^{20,21}

Food and Drug Administration Approval

In order for a medical device to be used in the United States, it must be approved by the FDA. Medical devices are divided into three classes for approval. Class I products are low risk, such as stethoscopes and gauze, and are exempt from approval. Class III devices are life threatening or life sustaining, such as defibrillators or pacemakers. Class II devices are a wide category of non-life-threatening or non-life-sustaining products. They still must meet approval, but through a much less stringent process known as the 510(k). Biologic meshes are considered Class II medical devices. To begin the approval process, a "Predicate Device," or a device that is similar to the

one seeking approval that has already been through the 510(k) approval process, must be identified. This is usually done through an online search of the FDA Product Classification Search Database. This will also generate a Product Classification code that can be used to determine if any special guidance documents, performance testing, or international standards apply to the product. If so, then these need to be met as part of the application process.

The new device is then compared with the Predicate Device. Once submitted, the FDA will review the device within 90 days and usually approve the device within 135 days. There is a fee associated with the submission. Once approved, the device is given a 501(k) number and must be registered with the FDA. The registration requires an annual fee paid to the FDA to maintain the 501(k) number.²² This is how many new biologic products are brought to market with no real evidence supporting their use. All biologic meshes are not created equal, and they may function very differently in vivo based on the method of processing. Although 510(k) approval may allow a product to come to market, it does nothing to prove the products efficacy.

Conclusion

The introduction of biologic mesh has given the surgeon many options for reconstruction in contaminated wounds. However, choosing the appropriate mesh remains a challenge. An improved understanding of the processes involved in preparing biologic mesh for human use allows the surgeon to make a more educated decision. Xenografts may present a more cost-effective option as compared with homografts and can be safely implanted without host rejection. Although cross-linking has been shown to increase initial mesh strength after implantation, this may be at the cost of increased inflammatory response to the mesh. The various tissue types vary in their strength and pliability, allowing the surgeon to tailor the mesh used to the application. The surgeon should consider the above factors, as well as the available data supporting the use of a particular product before implementing a new device into their practice.

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Suggested Readings

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