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The use of xenogenic dermal matrices in the context of open extremity wounds: where and when to consider?

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Summary: Optimal treatment of orthopaedic extremity trauma includes meticulous care of both bony and soft tissue injuries. Historically, clinical scenarios involving soft tissue defects necessitated the assistance of a plastic surgeon. While their expertise in coverage options and microvascular repair is invaluable, barriers preventing collaboration are common. Acellular dermal matrices represent a promising and versatile tool for orthopaedic trauma surgeons to keep in their toolbox. These biological scaffolds are each unique in how they are used and promote healing. This review explores some commercial products and offers guidance for selection in different clinical scenarios involving traumatic wounds.

Key Words: acellular dermal matrix, soft tissue injury, skin coverage, biological scaffolds

1. Introduction

Open limb trauma remains a relevant pathology in every orthopaedic trauma surgeon's practice. Despite ideal fixation of the underlying bony deformity, skin coverage remains paramount to a patient's recovery. Exposed bone, tendon, implants, and lack of soft tissue are challenging problems that can drastically impede wound closure. Inadequate skin coverage leads to issues such as postoperative wound dehiscence, infections, and chronic wounds from underlying deep infection. The methods currently used to achieve coverage include free, local or rotational flaps, split-thickness skin grafts (STSG), and negative pressure wound therapy (NPWT) to aid healing by secondary intention.[1] However, flap coverage is not always feasible due to limited hospital resources (eg, operating room availability, trained surgeons, staffing etc), while the others mentioned have been inconsistently successful with exposed tendon or bone.[2] Advancements in the management of open wounds have led to the development of biologic scaffolds to accelerate the healing process. This article reviews the types of engineered tissue products available and their relevance and success within open trauma to extremities.

2. Alternates

After thorough irrigation and debridement, the mainstay of treatment for traumatic soft tissue injuries includes the following:

- Split-thickness skin grafts (STSG)
- Tissue transplantation (ie, flap coverage)
- Dressing changes to promote healing by secondary intention such as wet to dry dressings or negative pressure wound therapy (NPWT)

When used appropriately in combination or isolation, these strategies can result in successful wound closure, typically over a prolonged period. However, many hospital-system, patient, and wound factors also influence this success rate, leading to uncertainty and anxiety for both surgeon and patient. Published literature shows that coverage with STSG alone in traumatic amputations is associated with significantly increased reoperation rates. Compared with delayed primary closure, amputees who received STSG were at higher risk for wound failure, need for heterotopic ossification excision, and soft tissue revision.[3] Not every wound is amenable to skin grafting. Exposed bone, tendon, cartilage, and implants lack the vascularity required to form granulation tissue. In these settings, traditional teaching recommends vascularized flap coverage, which is often expensive, intensive, and difficult to manage logistically if plastic surgery consultation is required.[4] In specific anatomic locations, such as the foot and ankle, flaps often create a bulky scar that may require revision to allow everyday footwear.[5] Flaps can also restrict mobility in the joint from the donor site leading to stiffness and decreased functional outcomes.[4] With exposed tendons, the inherent mobility creates an environment of chronic inflammation that impedes healing and leads to tendon necrosis. In these instances, dermal substitutes are an appealing adjunct or alternative.[2,5] Similarly, their use in exposed bone provides a protective barrier to the environment as periosteum and bone begin to reform.[6] Additional benefits include limited donor site morbidity, decreased wound contracture, and successful use in poor host patients too medically complex for autografting.[5]

3. Natural Biology

Wound closure aims to restore a barrier from the environment and return to normal function with minimal atrophy or scarring. To understand the mechanism by which engineered tissue accelerates

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wound healing, it is essential to understand the basic science behind the anatomy of the skin and the steps of routine wound healing. The gross layers of the skin are the epidermis, dermis, and subcutaneous tissue, disrupted partially or entirely by trauma. The type of wound healing is different depending on the level of injury. Partial thickness wounds include the mid-dermis and more superficial layers, which retain vascularity.[7] These wounds heal by re-epithelization from epidermal stem cells. However, deeper and more significant full-thickness injuries require the formation of granulation tissue which eventually epithelializes. For these injuries, wound healing consists of 4 phases: (1) hemostatic and inflammatory phase, (2) proliferative phase, (3) epithelialization, and (4) remodeling.[1] The hemostatic and inflammatory phase begins immediately after injury, as acute phase signals attract leukocytes, granulocytes, and cytokines to the injury site. Transition to the proliferative phase is driven by macrophages and the creation of granulation tissue. This transition is critical and dictates whether a wound will heal or persist as a chronic nonhealing wound. Granulation tissue consists of macrophages with their phagocytic and reparative properties, fibroblasts, blood vessels, and a matrix of type 1 collagen, glycoprotein, fibronectin, and hyaluronic acid. This granulation tissue is essential for connective tissue to heal by restoring vascularity to the injured wound bed. Finally, epithelial cells proliferate and migrate to cover the wound during epithelization. This process accounts for 80% of the final wound closure.[1] After epithelialization, the remodeling phase initiates the restoration of stem cells and the epithelium from the bottom up, creating a scar. Myofibroblasts drive this phase and create a smaller scar using contraction.[1]

4. Xenogenic Dermal Substitutes

Two major subcategories of tissue-engineered substitutes use different mechanisms to achieve wound coverage. Some work by providing substrate for the body's natural granulation tissue, thereby promoting formation. For example, porcine urinary bladder matrix (UBM) is a decellularized non–cross-linked extracellular matrix that triumphs in the coverage of large wounds, even when contamination or infection is present. UBM has been extensively studied as a substrate for regenerative medicine in the creation of engineered bladder, kidneys, heart valves, GI mucosa, and so on.[8–10] The porcine urinary bladder has several components that make it a successful tissue substitute, including a basement membrane that allows for proliferation and differentiation of epithelial cells, lamina propria, which induces angiogenesis, and type IV collagen, which accelerates closure. All components provide a scaffold that facilitates the ingrowth of vascular tissue over avascular structures. In addition to these components, the UBM has inherent antimicrobial properties. Basic science studies have shown that the breakdown products of UBM have antibacterial properties against Staph Aureus and E. coli.[11,12] Geiger et al[5] used UBM to manage culture-positive wounds, 100% of which achieved wound closure.[5,13] The ability to provide coverage and mitigate infection makes UBM a favorable option for managing traumatic wounds.[11] The mean time to complete healing is 26.5 weeks, with healing achieved after a median of 1.7 applications.[13] Currently, UBM comes in 2 forms—layered sheets and a particulate or powder—which can be used separately or together to achieve adequate wound coverage (Fig. 1). Fokin et al[14] describe a series of cases that used porcine UBM to cover lower extremity wounds that were unsuitable for other coverage methods. Porcine UBM, followed by STSG transplantation, successfully achieved soft tissue coverage in all these cases. Another study looked at UBM specifically for distal wounds with exposed tendons and found that it achieved adequate skin coverage and decreased periwound edema, drainage, and patient-reported pain. The average time to healing ranged from 9 weeks for exposed tibialis anterior tendon to 28 weeks for exposed Achilles tendon.[5]

Another method of achieving wound coverage may avoid the need for the time-consuming process of granulation tissue formation by creating a "neodermis" that can later be grafted upon. This "neodermis" provides the ideal scaffold for neovascularization and cellular repopulation needed for full thickness wound healing.[2,15] The neodermal skin produced at the end is clinically sturdier and aesthetically better than the scars left by secondary intention healing.[16] Commercial products using this strategy are composed from a wide range of materials with both synthetic and xenogeneic options covered in this review.

One synthetic scaffold is a benzyl ester of hyaluronic acid. Hyaluronic acid is a glycosaminoglycan (GAG) naturally found in human extracellular matrix.[2] Biologically, hyaluronic acid is integral to all stages of wound healing, including angiogenesis, cell proliferation, fibroblast migration, hydrodynamics, and stabilization of the wound.[2] In its esterified form, the hyaluronic acid acts as a three-dimensional scaffold that guides the reconstruction of the dermis. This product (Hyaff) comes in a bilayer dressing that can be trimmed to fit irregular edges of a wound. It also includes a protective silicone membrane with a similar vapor transmission rate to the skin. This additional layer helps hydrate the engineered tissue and prevents excess body fluid loss. Because it is an esterified synthetic product, it removes the risk of immunogenicity and may be more favorable in specific patient populations. Vaienti et al[17] 2013 investigated the use of esterified hyaluronic acid in the management of full-thickness wounds with exposed bone and tendons and found that in all cases, they had satisfactory tissue coverage, with 40% requiring a second application and 33% requiring an autograft to complete the healing. There was only one case of infection which delayed closure but was eventually attained. Another case series similarly looked at its efficacy and found that they achieved complete healing in 12 patients, all with exposed bone and tendon.[2] In this study, there were no instances of graft failure. Both studies emphasized the importance of close follow-up for wound evaluations to ensure that the graft and skin remain viable through the healing process.

A xenogeneic-based neodermis also comes as a bilayer construct with a bioengineered, cross-linked bovine collagen GAG matrix covered by a superficial silicone membrane. This product also limits myofibroblast infiltration and decreases wound contracture associated with disfiguration due to scarring.[16] Historically used in the management of burn wounds, its use has expanded to traumatic extremity wounds. Commercially known as Integra, this substitute comes in 2 different products: Integra Wound Matrix and Bilayer Wound Matrix. Wound Matrix and its bilayer counterpart are a porous matrix of cross-linked collagen. In the bilayer version, a semipermeable silicone layer helps keep the tissue hydrated until it is replaced with autograft. Unfortunately, both products require a second surgery which can be undesirable. Helgeson et al[16] used this cross-linked bovine tissue substitute followed by STSG to several lower extremity traumatic limb wounds with exposed tendon and bone and achieved successful coverage in 15 of 16 patients. The average time to STSG was 19 days after the application of the engineered tissue. In cases that failed, repeat grafting with collagen GAG matrix followed by STSG was successful.[4] Its use on upper extremities has been examined and was found to provide successful coverage with acceptable function and cosmetic

Generic Name	Brand Name	Form	Mechanism	# of stages	Advantages
Porcine urinary bladder (UBM): decellularized non crosslinked ECM	Acell Cytal®	Layers	Promotes granulation tissue	2	• Type IV collagen to accelerate wound closure • Lamina propria to induce angiogenesis • Antimicrobial properties • Can be used with other matrices • Low cost
	Acell MicroMatrix®	Powder			
Esterified hyaluronic acid	Hyalomatrix®	Hyaff-11® + Silicone membrane	Creates neo-dermis by providing scaffolding	2	Synthetic (eliminates potential issues with immunogenicity)
Bioengineered bovine collagen matrix	Integra Wound Matrix®	Matrix		2	Limits myofibroblast infiltration (wound contracture)
	Integra Bilayer Wound Matrix®	Matrix + semipermeable membrane			
Native bovine acellular dermal matrix	Integra Primatrix®	Matrix		1	• Limits myofibroblast infiltration (wound contracture) • One procedure • Type I and II collagen • Antimicrobial properties in Ag version

FIGURE 1. Description and names of common acellular dermal matrices.

appearance in 9/10 of their patients with exposed tendons and bone.[18] Integra manufactures another product, PriMatrix, which is an acellular fetal bovine dermal tissue matrix that can be used in a single procedure. This product similarly acts like a scaffold but also includes type 1 and 3 collagen and comes in an antimicrobial version (PriMatrix Ag) that holds infection-resistant properties. With this tissue product, re-epithelization can be seen in 4 weeks.

5. Instructions for Use

Appropriate acellular dermal matrix (ADM) product selection depends on patient and wound factors such as chronicity, vascularity, and exposed structures such as bone, tendon, or implant. Unfortunately, little evidence exists to guide this decision, beyond the commercial product descriptions and internal publications. It is the author's opinion that there is significant overlap and needless complexity in indications for use among these products. However, there are some basic principles for selection, illustrated in the cases and algorithm (Fig. 2) below, which have led to successful outcomes in the authors' experience. Absolute indications for ADM use include traumatic soft tissue wound beds with suboptimal location or vascularity which diminishes the likelihood of success with a local rotational flap or STSG, respectively. Relative indications include large defect coverage for patients with comorbidities who are poor candidates for a free flap, chronic or previously infected traumatic wounds without an active infection, and wounds that failed previous coverage attempts, thereby limiting tissue donor sites. The authors are cautiously optimistic about ADM coverage over exposed hardware; however, this indication requires further investigation because all ADM product technique guides list this as a contraindication for use.

There are certain fundamental surgical principles that must be applied in the setting of any traumatic extremity wound: (1) debridement of nonviable tissue, (2) optimization of vascularity, (3) prevention of additional trauma, and (4) reduction of mechanical shear stress.[1] Debridement is paramount to wound healing and requires necrotic or nonviable tissue excision.[19] In addition, primary wound closure is preferred over other methods and should be performed wherever in the wound it is possible. Dressing selection should be chosen in accordance with the specific wound properties (eg, necrotic, exudate, eschar, etc.) and is outside the scope of this review. In general, for most traumatic extremity wounds treated with acellular dermal matrices, the author prefers nonadherent, hydrating dressings, especially over ADM products without a semipermeable membrane. Many surgeons find that a combination of hydrogel, lubricant, and petroleum gauze is sufficient.[5]

A large portion of published literature on grafts and soft tissue substitutes reports NPWT to minimize shear forces and fluid accumulation.[5,14,16,20] Combined with UBM, NPWT can help maintain moisture and achieve stable granulation tissue even faster.[14] However, NPWT can be expensive and logistically challenging in the setting of outpatient management. Both published literature and authors' experience support successful wound coverage using ADM products without NPWT. Geiger et al[5] found that UBM retained moisture incredibly well for patients without NPWT, instead applying saline and hydrogel to the wound daily with dressing changes every 2–3 weeks. In all settings, frequent wound checks and dressing changes are required postoperatively. Most studies report wound and NPWT changes as regularly as 3–4 days.[16] One reason for these frequent wound checks is the "wound slough" that becomes apparent through the dressing. In standard wound care without ADM use, this slough is debrided to permit granulation tissue formation. However, it is important to leave this "slough" alone when using ADM products because it helps

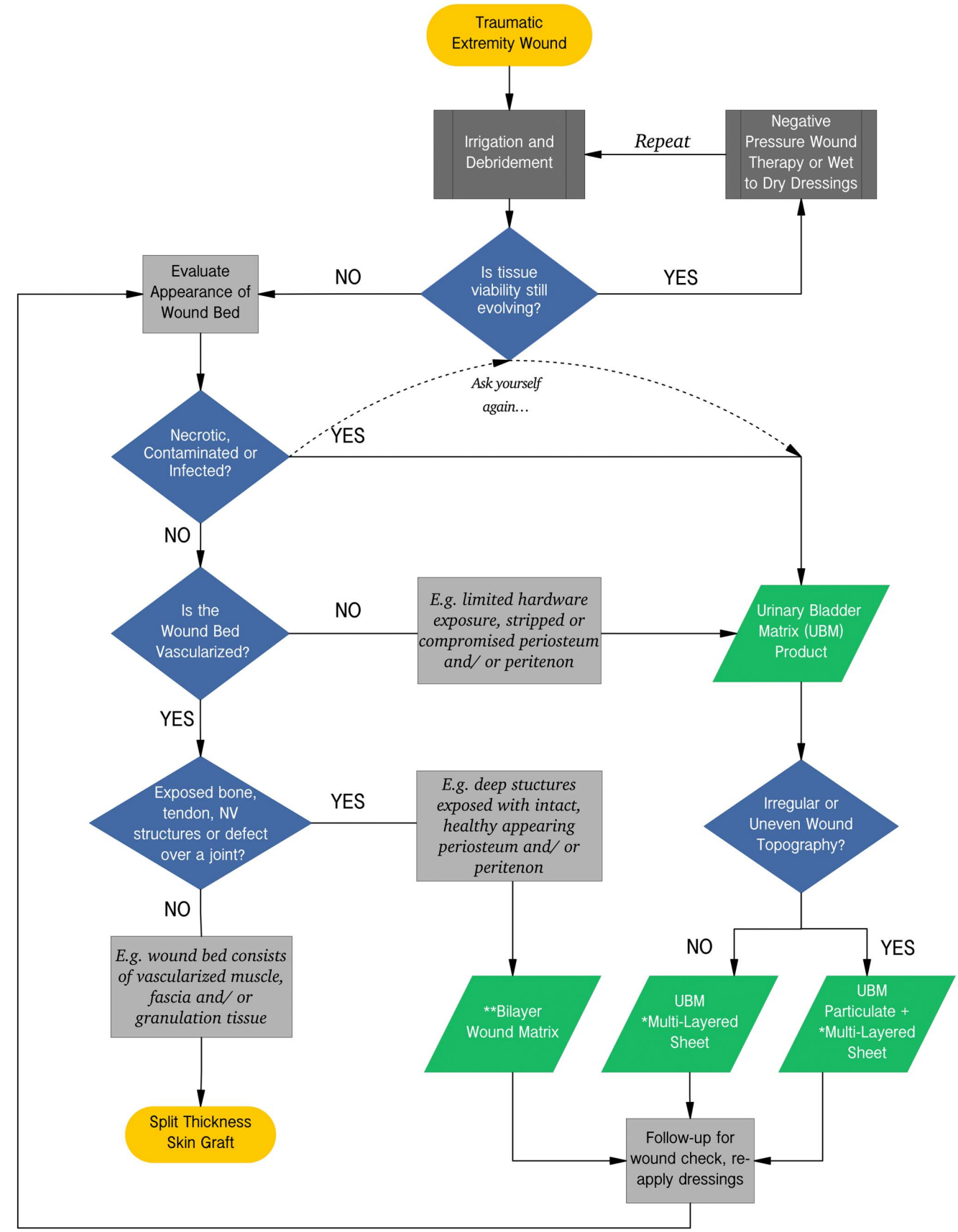

FIGURE 2. Decision-making flow diagram for selection of xenogenic dermal substitutes in the management of traumatic extremity injuries.

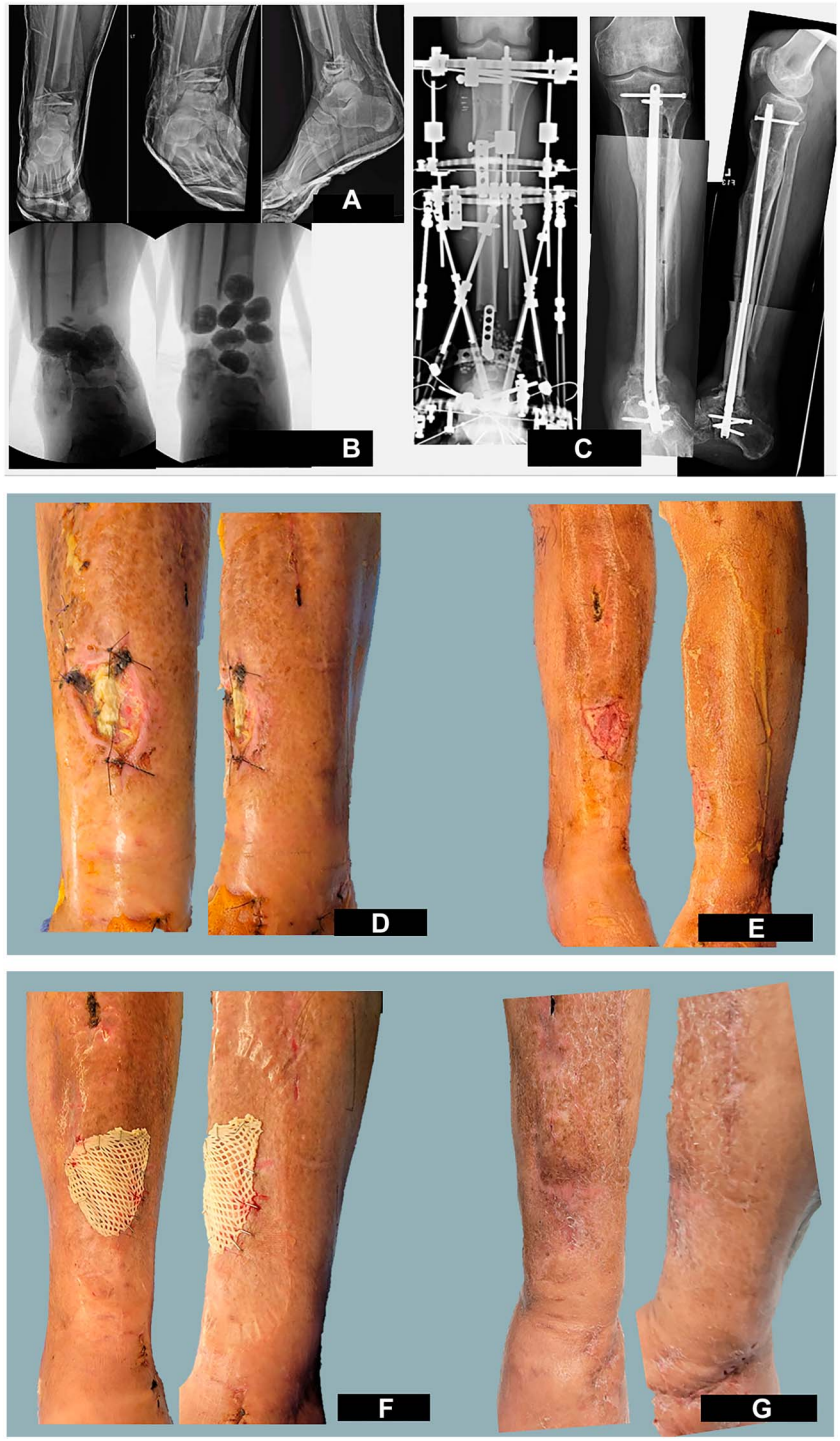

FIGURE 3. A, AP and lateral views of initial injury treated with (B) serial debridements and antibiotic bead placement with external fixation. Definitive fixation was performed with (C) distraction osteogenesis in a circular external fixator for several months followed by intramedullary nail placement across the docking site. After circular frame was removed, (D) a chronic wound with exposed bone was present on the anterior tibia. Aggressive debridement was performed initially, and bone vascularity was noted to be poor. Porcine urinary bladder matrix (UBM) powder was first placed followed by layered UBM and left in place for 3 weeks, resulting in (E) a healthy layer of granulation tissue filling the wound bed. After gentle irrigation and debridement, (F) a split thickness skin graft was applied. G, The anterior tibia defect was completely healed without complications of infection or need for further ADM application.

incorporate the matrix into the native wound bed and therefore should not be debrided.[20] The authors will generally see patients back 1 week after application because of logistics of clinic scheduling, and this time frame seems acceptable in our experience, however, following the specific ADM product guide recommendations when first implementing is advised, with minor protocol adjustments as needed as you become more comfortable working with the products. Adequate education must be given to

the patients and clinicians performing the wound check and dressing changes. The authors do not routinely immobilize patients solely for wound coverage with ADMs; fracture classification and treatment strategy drive this decision.

6. Case

It is important to remain agile when evaluating options for skin coverage. At our institution, the authors strategically use ADM products in combination with standard wound care strategies simultaneously or in sequence for successful coverage and healing of traumatic wounds.

A 60-year-old man in a motor vehicle collision sustained a Gustilo-Anderson type 3 open pilon fracture that required multiple trips to the operating room for irrigation and debridement with antibiotic bead placement (Fig. 3A). After physiologic stabilization, he underwent distraction osteogenesis through circular multiplanar external fixation (Fig. 3B), followed by intramedullary fixation spanning the ankle joint to allow for early stabilization of the docking site, quicker frame removal, and immediate weight-bearing (Fig. 3C). Although the fracture was stabilized, he developed a chronic wound on the anterior aspect of his tibia with exposed bone (Fig. 3D). After aggressive debridement, the bone was noted to have poor vascularity without much bleeding bone at the base of the wound. Given the wound's location, chronicity, exposed bone, and limited vascularity, the authors applied powered UBM (Acell Micromatrix) followed by layered UBM (Acell Cytal) at the time of initial debridement. After 3 weeks, the patient was brought back to the operating room, the silicone layer of Cytal was removed, and a healthy layer of granulation tissue was seen in the wound bed (Fig. 3E). At this point, a split-thickness skin graft (Fig. 3F) was applied. The patient continued to be followed closely and fully healed his anterior tibia wound (Fig. 3G).

7. Discussion

There are a variety of indications for these engineered tissue substitutes, and the type of product used is often determined by wound characteristics (Fig. 1). The authors proposed a nonexhaustive algorithm for their application in the setting of traumatic extremity wounds (Fig. 2). First, it involves careful inspection of the wound base in the operating room, considering the nature of the original insult. In a clean wound with a healthy vascular wound base, one can proceed with STSG. A contaminated wound with a compromised wound bed is a reason for caution. Any wound with threatened soft tissue, exposed tendon, bone, or hardware often does not do well with STSG. In these situations, the authors recommend UBM particulate (Acell Micromatrix) followed by the layered formulation (Acell Cytal). After 1–2 weeks (or more), the wound bed is reevaluated. If there is healthy, clean granulation tissue, the next step is to proceed with STSG. However, if the wound bed still shows concern and requires further structure, the authors proceed with ADM placement. After this step, we recommend proceeding with STSG at an appropriate time as determined by the surgeon. Authors are trending toward waiting even longer between ADM application and skin graft. During this time frame, smoking cessation and supplementation with immunonutrition products are recommended for decreased complications and optimized wound healing.[21]

The authors generally do not acutely skin graft, although, in some patients, it would be favorable to do so. In addition to coverage for a traumatic wound, the authors found it beneficial to use a single layer of bioengineered bovine collagen matrix (Integra Thin). For the dressing, there are different options depending on the desired frequency of wound checks and dressing changes. In patients with close follow-up (3–4 days), a single sheet of nonadherent petroleum impregnated mesh gauze is sufficient. In settings where follow-up duration is extended, a more hydrating dressing can be used, consisting of 2 sheets of nonadherent petroleum impregnated mesh gauze with a healthy amount of lubricant between them. NPWT is infrequently used to facilitate outpatient surgical management and minimize obstacles to discharge for inpatients.

A potential disadvantage to using tissue-engineered substitutes is cost per use. Although the cost of these products may initially seem high, their use is associated with decreased trips to the operating room, which is a costly expenditure for the patient. For example, one cost analysis study compared total costs in patients treated with a dermal substitute with patients who received a skin graft. Although the initial cost of the dermal substitute group was higher, there was no statistically significant difference between the 2 groups when indirect health costs such as length of stay were factored in.[22] In addition, there are some aspects of the tissues themselves that pose limitations. For example, engineered tissue lacks sweat glands and hair follicles, which can affect the cosmetic appearance of the healed wound. There is also variability in the completeness of sensation restoration.[4] This is important when addressing traumatic wounds to the volar hand and fingertips.[20] Another consideration is accounting for patient allergies to bovine, chondroitin, and silicone, which can cause a local inflammatory reaction which would be counterproductive to wound healing.[23]

Traumatic wound management often requires creative and innovative coverage strategies. Acellular dermal matrices are a helpful tool to accelerate wound healing and can also be considered in dire or salvage situations. With the advent of tissue-engineered substitutes, a wide variety of wound coverage options are available to surgeons. Hallmark skin coverage techniques have ranged from thin epidermal coverage using STSG on a healthy vascularized wound bed to deep rotational and free flaps which provide more robust coverage to compromised wounds with exposed hardware, bone, or tendon. Tissue-engineered substitutes fit nicely between these two options offering surgeons greater flexibility and customizability to suit each traumatic wound.

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