Abstract: Introduction. Treating difficult-to-heal wounds with complexities, including those with exposed tendon/bone or infection, is a challenge that regularly confronts practitioners in a variety of clinical environments. The purpose of this study was to review the effectiveness of an acellular fetal bovine dermal repair scaffold (PriMatrix Dermal Repair Scaffold, TEI Biosciences, Inc, Boston, MA) used to treat complex difficult-to-heal wounds presenting in the authors’ practice. Methods. A retrospective chart review was conducted of a single practice with multiple practicing physicians between 2008 and 2010. Over this time period, 70 patients with 83 wounds were treated with the acellular fetal bovine dermis following surgical debridement of the wound. Forty-nine patients (58 wounds) met established inclusion/exclusion criteria and were critically evaluated. Results. Wounds treated with the acellular fetal bovine dermis included chronic diabetic wounds, venous wounds, and pressure ulcers, as well as wounds caused by trauma and surgery. Additionally, the patients treated had comorbidities commonly associated with recalcitrant wounds. Of the wounds evaluated in this study, 75.9% successfully healed; 63.8% reepithelialized, and 12.1% were closed with a skin graft subsequent to treatment. Notably, the majority (58.6%) of the wounds reepithelialized by 12 weeks following a single application of the dermal repair scaffold. In the subset of challenging wounds with exposed tendon/bone, 80.8% of the wounds were treated successfully (61.5% reepithelialized, and 19.3% were skin grafted), indicating the successful regeneration and reepithelialization of new vascularized tissue by fetal dermal collagen in relatively avascular wound defects. Conclusion. The acellular fetal bovine dermal repair scaffold can be used as part of an effective treatment regimen to heal complex wounds with exposed tendon/bone caused by varying etiologies. The product actively participates in the generation of a new, vascularized tissue capable of reepithelializing, or successfully supporting, a split-thickness skin graft in defects where initial grafting or living skin substitutes are not viable options.

Surgical debridement to remove necrotic or infected tissue from chronic wounds can result in challenging skin defects that are unable to be closed primarily, and are unresponsive to secondary or tertiary healing modalities. Similar difficult-to-heal, full-thickness wounds...
are often presented subsequent to trauma, burns, or the surgical removal of cancerous lesions. Wound size, depth, and exposure of relatively avascular tendon, fascia, bone, and capsular tissues can all contribute to wound complexity.\(^1\)

Decellularized mammalian tissues that retain extracellular matrix components (ie, collagens) have recently been reported to be an effective clinical strategy to treat difficult-to-heal wounds.\(^2\)–\(^6\) Making generalizations as to their clinical effectiveness, however, has been difficult, as such products vary widely in processing, composition, structure, and biological response.\(^7\)–\(^9\) The authors chose to use an acellular fetal bovine dermal repair scaffold (PriMatrix Dermal Repair Scaffold, TEI Biosciences, Inc, Boston, MA) to treat difficult-to-heal wounds based on its unique composition of type I and type III collagen found only in fetal tissue.

During fetal development, and in healing cutaneous wounds, relatively high levels of type III collagen are present. In fetal dermis, type III collagen comprises approximately 30% of the total collagen, whereas in adult skin, it comprises 10% or less.\(^10\),\(^11\) Notably, only fetal tissues having such a unique collagen composition have been found capable of healing without scar tissue formation.\(^12\),\(^13\) The predominance of type III collagen in the early phases of adult cutaneous wound healing has long been appreciated.\(^14\)–\(^16\) In the proliferative phase, type III collagen increases to 30% of the total collagen content. Wound healing experiments with adult mice genetically deficient in type III collagen demonstrated that diminished or low levels of type III collagen during wound healing results in increased scar formation and decreased tissue regeneration.\(^1\) Type III collagen, or, more specifically, the ratio of type III to other collagens, appears to be a key mediator and contributor to skin tissue development, healing, and regeneration.

Published case studies and case series illustrate the clinical utility of the fetal dermal collagen scaffold technology. The scaffold was reported to successfully augment secondary closure of a full-thickness skin injury with exposed bone and tendons following a crush injury.\(^1\) In another case presentation, sheets of the scaffold were stacked to fill significant tissue voids. The implanted dermal scaffolds provided tissue bulk, and eventually supported a delayed skin graft in the effective treatment of a significant tissue deficit following aggressive debridement in a necrotizing fasciitis case.\(^1\) A case series on deep dermal wounds reported faster healing with reportedly less scarring when compared to treatment with negative pressure wound therapy (NPWT).\(^2\) To date, the largest case review published on fetal dermal collagen treatment compared outcomes of diabetic foot and venous leg ulcers treated with either fetal dermal collagen or a living skin substitute. The fetal dermal collagen was found to heal both ulcer types approximately twice as fast as the living skin substitute.\(^2\)

The fetal bovine dermal repair scaffold, which is derived from fetal bovine dermis, was adopted by the authors’ practice with the goal of healing wounds that had failed to heal using conventional treatments. When primary wound closure was not an option, and skin defects failed to reepithelialize, aggressive surgical debridement was performed and the dermal repair scaffold was fixed into the wound bed. The product was observed to incorporate into the wound as reepithelialization progressed. In some circumstances, a delayed skin graft was applied to the wound bed with incorporated dermal repair scaffold to achieve definitive closure. This study reports the authors’ initial experience with this technology in complex, difficult-to-heal wounds, presenting detailed descriptions of the patient population, comorbidities, wound characteristics, treatment regimens employed, treatment outcomes, and treatment recommendations.

**Methods**

**Study setting and design.** A retrospective chart review was conducted to identify patients that had received the fetal bovine dermal repair scaffold from January 2008 through January 2011. This included all patients treated by the authors across multiple sites where the authors care for patients. The data was collected under an Institutional Review Board-approved protocol, and 70 patients with 83 wounds were identified as having been treated with the dermal repair scaffold.

**Fetal bovine dermal repair scaffold treatment.** Wounds were surgically debrided to clear the area of
debris, necrotic tissue, and contaminated/infected tissue. This site preparation included deep debridement to ensure healthy bleeding wound edges containing viable tissue. For wounds being treated for acute infection, all infected tissue was removed, including areas of spongy bone when osteomyelitis was confirmed. Following debridement, infected wounds were thoroughly cleansed by lavage with antibiotic solution.

For all patients, the dermal repair scaffold was applied in the surgical setting using sterile technique. The scaffold was rehydrated in 0.9% sterile saline at room temperature, and in instances where acute infection was being concurrently treated, the product was soaked in a triple antibiotic solution composed of gentamycin, clindamycin, and polymyxin. Typically, the dermal repair scaffold was meshed or fenestrated to allow fluid drainage from the wound site, as well as to allow enhanced contouring of the scaffold to the wound bed. After the scaffold was secured to the wound bed using suture or staples, secondary dressings were applied. These included a non-adherent layer, followed by petrolatum gauze, and a layer of dry sterile gauze, all of which were wrapped in gauze roll and self-adherent elastic wrap.

Wounds were also treated with standard protocols specific to the wound type including offloading devices and compression. In a small subset, NPWT was used concurrently with the dermal repair scaffold in wounds that had large tissue deficits, or in patients with exposed tendon and/or bone. Secondary dressings were changed as needed, typically at least once a day, with no disruption of the dermal repair scaffold. Wounds were clinically reassessed weekly.

Data collection. Medical records were reviewed and details were compiled by a sole data collector. Demographic data (ie, age, sex, weight, and comorbidities) were recorded for patients treated with the dermal repair scaffold. Wound history (ie, size, age, and previous treatments) was also reviewed and recorded. In order to uniformly describe the severity of the lower extremity wound, it was classified as superficial, penetrating to tendon or capsule, or fully penetrating to bone or joint. Whether infection or ischemia was present was also noted. Patient progress over the treatment course was recorded, including time-to-healing, and any postoperative complications, such as infection or patient non-compliance.

Wound healing analysis. For the 83 wounds identified as being treated with the dermal repair scaffold, wounds were excluded from analysis if 1) the patient was lost to follow-up (13 wounds), 2) the patient died during treatment from complications or diseases that were unrelated to the wound treatment (4 wounds), or 3) treatment irregularities or inconsistencies were noted (eg, the patient displayed extreme noncompliance during treatment (5 wounds); or the dermal repair scaffold was mistakenly removed during a dressing change by a nurse or other medical professional (3 wounds).

Forty-nine patients with 58 wounds met the stated study inclusion/exclusion criteria and were analyzed. For wounds healing by secondary intention, a healed wound was defined as complete wound reepithelization as assessed by the treating personnel and recorded in the patient’s medical record. A wound was also defined as healed if closure was achieved by skin grafting onto the wound treated with dermal repair scaffold. Time-to-healing analysis could be performed on a subset of 29 wounds where reepithelialization was confirmed and the patients returned for routine follow-up visits.

Results

Wound etiology, patient comorbidities, and wound complexities. Of the patients treated with the fetal bovine dermal repair scaffold, 49 patients with a variety of 58 wounds met the inclusion/exclusion criteria. Eleven patients had 12 diabetic foot ulcers, 5 patients had 8 venous stasis ulcers, 10 patients had 13 pressure ulcers, 13 patients had 13 surgical wounds, 9 patients had 10 wounds of traumatic origin, and 1 patient had a pressure ulcer and surgical wound. Figure 1 displays the percentage of wounds treated with the dermal repair scaffold.

Patient comorbidities in the treated population were significant, numerous, and are known to adversely impact wound healing (Table 1). Type 2 diabetes was diagnosed
in 63.3% of the treated patients, peripheral vascular disease (PVD) in 63.3%, and neuropathy in 61.2%. Osteomyelitis was noted in 36.7% of the patients treated with the dermal repair scaffold, and a relatively small number of patients had been diagnosed with chronic renal failure (12.2%), and/or had a previous bypass graft (14.3%).

In addition to the numerous patient co-morbidities, many wounds had exposed tendon and bone, and/or were being treated for infection (Table 2). Overall, 42 of the 58 wounds had complexities, with 7 wounds having only exposed tendon and/or bone; 16 wounds having only infection; and 19 wounds having both exposed tendon and/or bone plus infection. Surgical wounds had the greatest number of added complexities, followed by diabetic foot ulcers and trauma wounds. Ischemic wounds were not prevalent in this population (3 of 58 wounds).

**Keypoints**
- Of the patients treated with the fetal bovine dermal repair scaffold, 49 patients with a variety of 58 wounds met the inclusion/exclusion criteria.
- Wound healing was evaluated for 58 wounds; 44 (75.9%) healed with the fetal bovine dermal repair scaffold (Figure 3). Of the wounds that healed, 63.8% reepithelialized, and 12.1% were definitively closed with a skin graft placed onto the vascularized tissue bed generated with the dermal repair scaffold product.
- The overall healing percentage with the use of the dermal repair scaffold plus NPWT was 68.8% (11 of 16). For reference, the healing percentage of the wounds treated with the dermal repair scaffold alone was 78.6% (33 of 42).
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percent of wounds treated with the dermal repair scaffold healed by etiology (Figure 3), it was found that surgical wounds, trauma wounds, and pressure ulcers all healed in more than 75% of the cases. Diabetic ulcers were found to have a healing percentage of 50%, and venous stasis ulcers of 62.5%.

Time-to-healing analysis of all wounds indicates that, of the patients that healed by secondary intention, the majority, 19 (65.5%) reepithelialized by 12 weeks; by 15 weeks, 25 (86.2%) of the wounds reepithelialized; and after 6 months, all but 2 of the remaining wounds reepithelialized (Figure 4).

When evaluating the healing percentages for the subset of wounds with identified complexities (Table 2), it was found that 84.2% (16 of 19) of wounds with both exposed tendon and/or bone plus infection healed; 50% (8 of 16) of wounds that were only infected healed; and 71.4% (5 of 7) of wounds with only exposed tendon and/or bone healed. When combining all wounds with exposed tendon and/or bone, 80.8% (21 of 26) healed.

Negative pressure wound therapy was used as an adjunctive therapy to the dermal repair scaffold for 16 (27.6%) of the 58 wounds. Of these 16 complex wounds, 5 (31%) had exposed tendon and/or bone; 4 (25%) were infected; and 7 (43%) had exposed tendon and/or bone plus infection. The majority of the wounds treated with the dermal repair scaffold and concurrent NPWT were diabetic foot ulcers (6 of 16) and surgical wounds (6 of 16). The overall healing percentage with the use of the dermal repair scaffold plus NPWT was 68.8% (11 of 16). For reference, the healing percentage of the wounds treated with the dermal repair scaffold alone was 78.6% (33 of 42).

**Discussion**

This retrospective analysis of the fetal bovine dermal repair scaffold is the largest study of this product to date and supports its continued use to treat complex, difficult-to-heal wounds. Overall, the authors found that 75.9% of the wounds healed, with 58.6% of the wounds reepithelializing by 12 weeks, following a single application of the dermal repair scaffold. Although the results and discussion are limited to descriptive statistics per the limitations of a retrospective study lacking a control group, this work documents that healing was observed in the majority of complex recalcitrant wounds of varying etiologies when the scaffold was added to the treatment regimen.

The authors used the scaffold as an adjunct to a standard therapeutic treatment regimen. In the authors’ practice, the initial treatment of each wound consists of an aggressive surgical debridement to remove necrotic tissue, reduce bioburden, and assist in converting the chronic wound to an acute wound to initiate the process of wound healing. After debridement, the dermal repair scaffold was placed into the wound bed and was found to be compatible with existing standard protocols for moist infected wounds.

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wound therapy (petroleum gauze) or NPWT. Through the authors’ analysis, it was determined that similar populations of patients were treated with the dermal repair scaffold and with the scaffold plus NPWT. When the wounds were independently evaluated for healing, similar results were found in the wounds treated with the dermal repair scaffold and in the wounds treated with the scaffold plus NPWT, with 33 (78.6%) and 11 (68.8%) healing, respectively.

It is believed that NPWT was an excellent technique to anchor the scaffold to the wound bed, control exudate in the wound environment, and help with patient compliance during wound treatment.

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These study results are consistent with published literature reporting the dermal repair scaffold plays a role in the generation of tissue in complex wounds, and is capable of reepithelializing or successfully supporting split-thickness skin grafts.21–23 The authors’ clinical observations and published literature suggest the dermal repair scaffold works in conjunction with mechanisms associated with the process of wound healing. Immediately after application of the scaffold into the acutely debrided wound, the authors noted rapid absorption of blood into the implant, and the stabilization of the developing fibrin clot by the collagen fiber framework. When filled with the blood clot, the collagen scaffold sequestered an initial cell population, including progenitor cells and activated platelets known to release growth factors associated with cellular migration, proliferation, and angiogenesis. It was also noted that, in contrast to other processed dermal collagen, the fetal bovine dermal repair scaffold has been reported not to elicit an acute or chronic inflammatory response when implanted.8,9,25,24 The technology used to process the fetal bovine dermis does not alter the native biochemistry of the collagen molecules, thus rendering it immunologically indistinguishable from host collagen.9 In addition, the same fetal collagen fiber preparation has been shown histologically to support cellular repopulation and revascularization, generating a new dermal-like tissue when placed into a full-thickness wound.25 This was particularly evident in the authors’ experience using the dermal repair scaffold to treat wounds with exposed tendon and/or bone. The authors observed the generation of vascularized tissue in the defects and the successful closure of the wounds by reepithelialization or use of a split-thickness skin graft.

Future studies of the dermal repair scaffold might consider prospectively comparing the use of this wound healing technology as an initial treatment regimen for similar, recalcitrant wound types against moist wound therapy alone to fully elucidate its efficacy over the standard treatment regimen. In addition to clinical outcomes, such studies could also systematically evaluate the relative economic benefit to the patient, wound care center, and third party payer. As current fee-for-service reimbursement practices are being reevaluated, formal analyses of whether added initial costs of advanced technologies decreases overall expenditure by improving wound healing outcomes is of increasing interest.

Conclusion

An acellular fetal bovine dermal repair scaffold can be used in conjunction with moist wound therapy or NPWT regimens to heal recalcitrant wounds of varying etiologies. The study found the scaffold actively participated in the generation of vascularized tissue over full thickness defects containing exposed tendon and/or bone where initial grafting or use of living skin substitutes were not viable treatment options. Furthermore, the vascularized tissue was capable of reepithelializing or successfully supporting a split-thickness skin graft to achieve definitive closure of the wound.

References

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