The Shift to Synthetics: A Review of Novel Synthetic Matrices for Wound Closure

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ABSTRACT

Since the late 1990s, a growing number of "skin substitutes" have become available to practitioners seeking to heal large surface wounds. These extracellular matrices were originally from xenograft sources, and then from very highly engineered living human cellular tissues. More recently, they consist of biosynthetic materials that are combinations of silicone, collagen and chondroitin. The list of xenograft materials as well as minimally manipulated human tissues, such as human skin-, amniotic- and placental-based products, has grown exponentially. Over the last 5 years, truly synthetic materials have become part of the armamentarium available for closing large wounds. The first notable product in this category was made of polyurethane. These purely synthetic products do not have any components made of naturally occurring structures, such as collagen. In this review, we seek to create a rudimentary framework in which to understand these synthetic products and to review the current literature that supports the use of these novel yet intriguing therapies.

INTRODUCTION

Large surface wounds remain a challenge for practitioners to close despite the availability of numerous advanced treatments. Various "skin substitutes" or wound matrices are now often used for the regeneration of dermal and epidermal layers. These are predominantly composed of biologic materials such as processed xenogeneic and allogeneic tissues. However, biologic wound matrices have limitations, such as variable durability and longevity, the potential to elicit an immune or inflammatory response, inconsistent compositions, and usually high costs.[1]

Human extracellular matrix is a three-dimensional network made up of collagen, glycoproteins and enzymes to which cells adhere. This scaffold is critical for cells to organize and communicate, thus allowing the healing process to progress. Stagnation in the healing process can be attributed to a lack of robust extracellular matrix deposition and cellular ingrowth as well as inadequate blood flow and disturbances in the environment, such as in the pH, bioburden or an excessive immune response.[2]

New synthetic matrices have the potential to address many of these causes of poor wound healing. Whether in powder, gel or sheet form, these matrices assemble into a dermal scaffold like a native extracellular matrix, which can be integrated as neodermis. These synthetic wound matrices are compatible with human cells and avoid any risk of disease transmission. There is more control over their composition and mechanical properties, so that their degradation can be

somewhat controlled, which is often not possible with highly processed biologics.[3] Several of these synthetic options contain polylactic acid, which lowers the pH of the wound bed as the matrix degrades, thus promoting angiogenesis, increasing oxygenation to the tissues and hampering destructive inflammatory processes.[4] Additionally, they can be engineered with additives like antimicrobial silver or pro-regenerative boron to facilitate better wound healing. In addition to these advanced unique features of each matrix, they all must still serve fundamental roles in wound healing, like managing the moisture balance and acting as a protective barrier.

The synthetic matrix market has suddenly blossomed and claims to provide a superior temporary microenvironment that encourages endogenous wound healing. Will there be a major shift towards synthetics? In this review, we present the various types of synthetic products available and the clinical literature supporting their use.

NovoSorb® BTM (PolyNovo)

NovoSorb® BTM (PolyNovo Ltd, Port Melbourne, Victoria, Australia) was one of the first completely synthetic extracellular matrix products on the market. It is a temporizing scaffold made of biodegradable polyurethane and is indicated for use in the management of all types of wounds. Its intended purpose is to serve as the first step of a two-stage approach to close wounds. After debridement, the synthetic matrix (BTM) is applied, which helps to encourage cell proliferation and neovascularization of the wound bed in preparation for the second stage, an autograft.

Since 2006, all initial studies were to prove the biocompatibility and safety of BTM both in vitro in cell cultures [5,6] and in studies in vivo.[7] The polymer was implanted subcutaneously in rats and was shown to have no systemic or local toxic effects. In surgically created full-thickness wounds in sheep, application of BTM promoted integration of the matrix and resistance to contraction. Next, multiple optimization studies were performed in porcine wound models, which helped expose the need for a second layer on the polyurethane matrix to provide a seal to the porous scaffold to prevent contraction, excessive evaporative water loss, and tissue overgrowth.[8] BTM fared well in a small side-by-side comparison to Integra® dermal regeneration template (Integra LifeSciences, Plainsboro, NJ) in a porcine model, in which there were no incidences of infection and less wound contraction.[9]

Based on the initial human trials, the product, which was now a bi-layered matrix made up of a 2mm-thick foam degradable by hydrolysis and a non-biodegradable polyurethane film on the superficial surface that was meant to be peeled away before autografting (Fig. 1), required one more modification. In a small study of long-term implantation of BTM in free-flap donor site wounds, it was realized that the material seal needed fenestration.[10] In subsequent studies using BTM in 10 additional free-flap patients or in 5 patients with 20–50% total body surface area (TBSA) full-thickness burn wounds, it served as an effective temporary dermal matrix that bridged large or contaminated wounds to split-thickness skin grafting (STSG) and had favorable scar outcomes.[11,12]

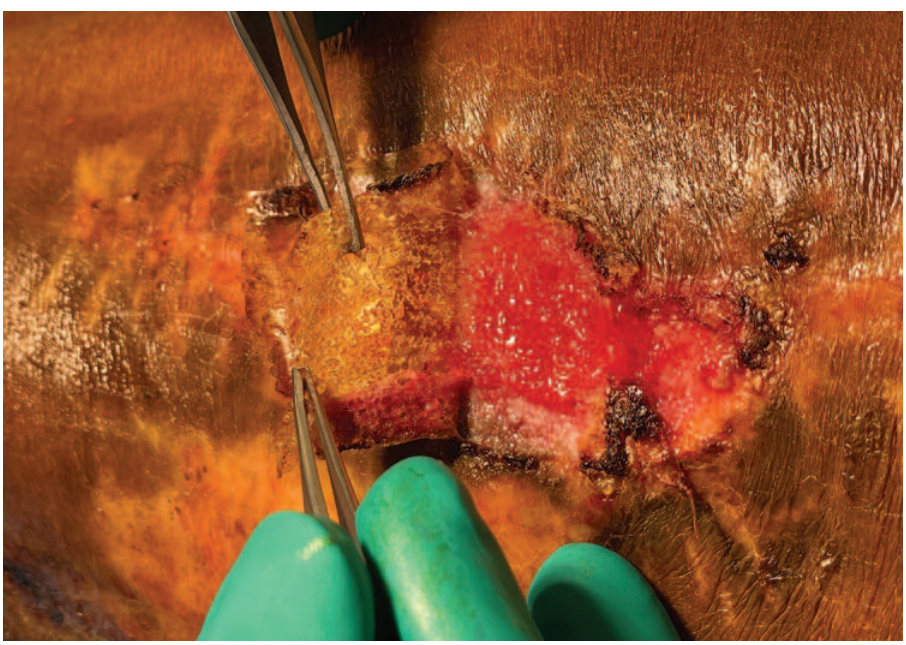

Figure 1. Non-biodegradable polyurethane film of BTM peeling off prior to autografting.

All of these studies were performed by the same group of product developers, which allowed for perpetual improvements and alterations. Fortunately, consistently positive outcomes were seen in trials by other clinicians. Frost et al. observed the formation of a robust "neodermis" with BTM prior to STSG for foot and ankle wounds and no loss of functionality despite spanning a joint.[13] Concannon et al. had success with BTM followed by STSG in treating an extensive perineal burn wound, where healing of the complex anatomy is further disadvantaged by its unfavorable microbial environment.[14]

In slightly larger studies, Solanki et al. trialed BTM in 25 patients with complicated wounds of all etiologies but with a majority involving bone or tendon, and concluded it was a good reconstructive option to bridge to definitive closure. While infections occurred with use of the matrix, unlike their experience with many other biological dermal matrices, wounds with BTM could often be salvaged.[15] Li et al. used BTM on 35 complex wounds before performing STSG 3-4 weeks later All but two of these wounds had 100% incorporation of BTM, leading to successful graft take outcomes.[16] A retrospective cohort study compared 55 patients with at least 40% TBSA who received BTM (n=22) versus cadaveric allograft (n=33) as a temporizing measure for full-thickness burns. Clinical outcomes were similar in the two groups except that those treated with BTM had a significantly shorter operative time.[17]

There have been a few reports on deviation from the recommended two-stage approach with BTM.[16,18,19] Wounds were allowed to heal by secondary intention after application of the matrix for various reasons such as medical instability. Although aesthetic outcomes were less favorable, BTM appeared to help produce a bed of healthy granulation tissue over which re-epithelization could occur.

Our experience with BTM has been described in a retrospective review of 12

very ill patients who had exposed structures including tendon and nerve.[20] They were all debrided in the operating room with tangential hydro surgery, and covered with open cellular polyurethane foam and negative pressure wound therapy followed by skin grafting. The median age of the patients (8 women and 4 men) was 62 years. Four were white, 4 were black, and 4 were Latino. The median size of the wounds was 220 cm^2 and all 12 patients had greater than 85% granulation when the open cellular polyurethane foam was explanted (Fig. 2). The explantation date was day 21 and skin grafting (in 10/12 patients) was performed on day 28. One patient went on to receive an above-knee amputation due to ongoing pain, despite excellent granulation full tissue coverage on day 21. One patient did not go on to skin grafting for 2 months due to severe cardiac disease.

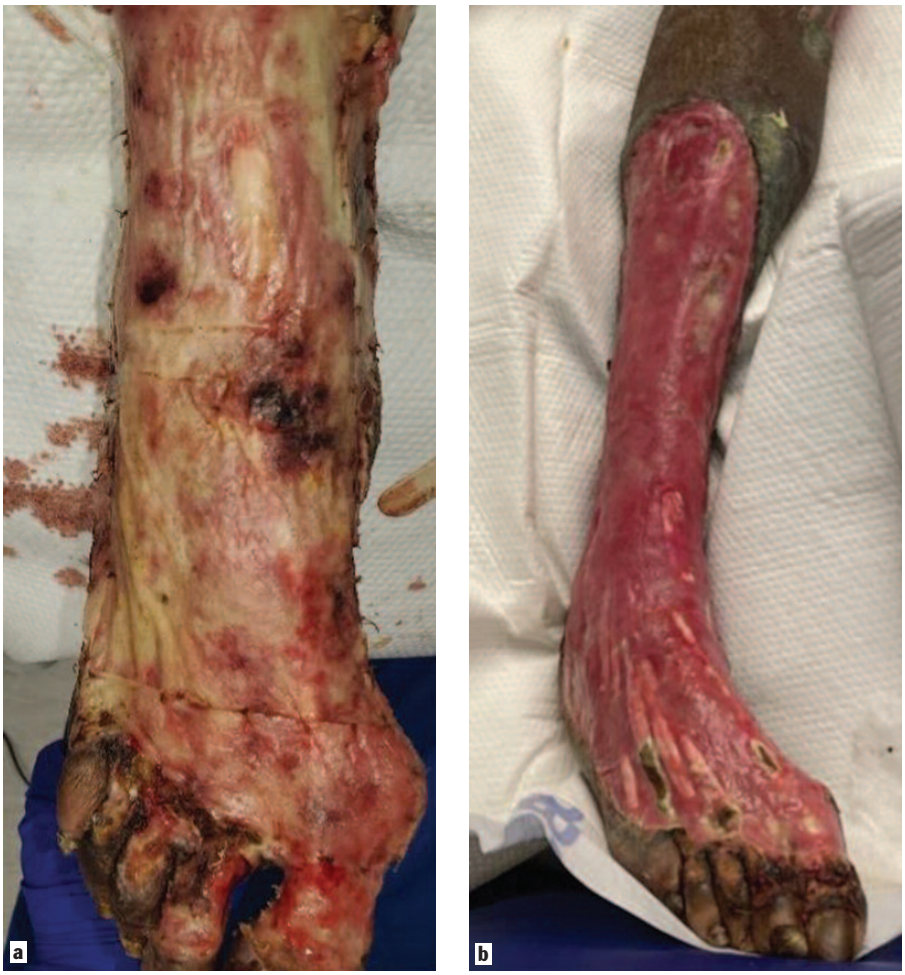

Figure 2. (a) Patient with calciphylaxis of a lower extremity with BTM applied. (b) After removal of BTM at day 20.

Suprathel® & Supra SDRM® (Polymedics Innovations; PMI)

Polymedics Innovations (Denkendorf, Baden-Wurttemberg, Germany) has two absorbable, synthetic matrix products on the market: Suprathel® and Supra SDRM®. Suprathel®, a microporous membrane intended as a translucent temporary secondary skin, was launched in Germany in 2004 and was approved by the FDA five years later. Supra SDRM®, an extracellular matrix, came to market in 2017. While the two products are made of similar components, their indications and structures vary slightly. They are both terpolymer products composed of polylactide, trimethylene carbonate, and ε-caprolactone. However, structurally, Supra SDRM® contains larger pores for cellular ingrowth and is specified as a dermal matrix for difficult to heal wounds (Fig. 3).

It has been found that acids released with breakdown of the product lower the pH of wounds to reduce matrix metalloproteinase (MMP) activity, improve tissue oxygenation and make for a less hospitable environment for microbes. Ring et al. demonstrated increased angiogenesis with the use of Suprathel® when implanted in skinfolds of mice.[21] Studies comparing Suprathel® to porcine-derived wound dressings in both animals with Biobrane® (Smith & Nephew, London, UK) [22] and in humans using Oasis™ (Cook Biotech, Inc., West Lafayette, IN)[23] have shown comparable outcomes.

Gürünlüoğlu et al. compared a hydrofiber with silver dressing to a

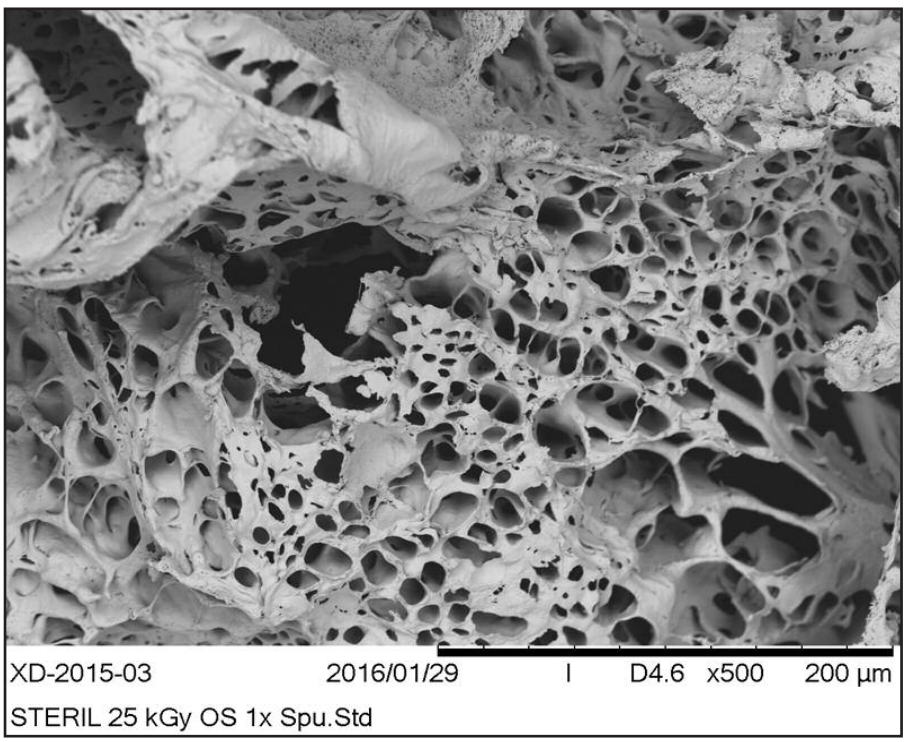

Figure 3. SEM of SDRM (Photo provided by and permission to publish from Polymedics Innovations).

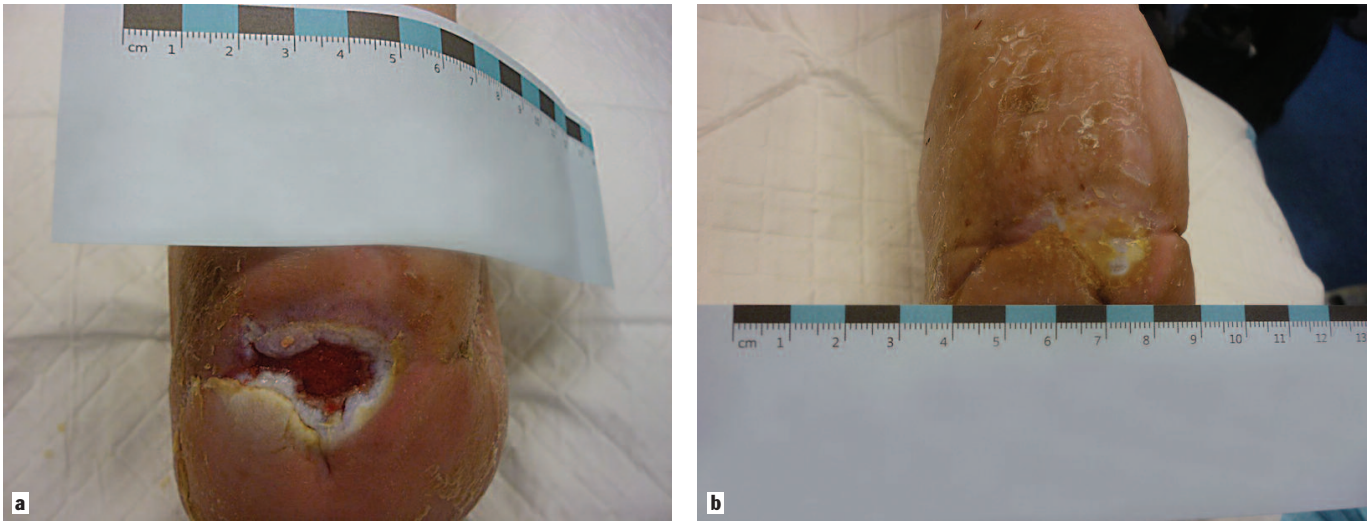

Figure 4. (a) DFU at week 0 and (b) week 6 after weekly applications of SDRM (Photo provided by and permission to publish from Polymedics Innovations).

Suprathel® dressing in pediatric burns and found that Suprathel® decreased levels of inflammatory markers like IL-6 and TNF-a.[24] There have been many studies on the application of Suprathel® to partial-thickness burn wounds touting clinical benefits like pain reduction, easy application, fewer dressing changes, good cosmetic outcomes and low complication rates.[25-28]

Far fewer data are available on Supra SDRM®. Four case reports collected and distributed by the manufacturer include two cases of diabetic foot ulcers (DFUs) on the heel (1.1cm^2 and 4.5cm^2) healing within 1 and 6 weeks, respectively (Fig. 4), as well as a complicated 25cm^2 deep surgical wound on the dorsal foot and a 12 cm^2 venous leg ulcer (VLU) completely healing within 12 weeks with weekly applications of Supra SDRM®.[29] A poster at the 2023 Spring Symposium on Advanced Wound Care (SAWC) presented a pilot RCT that compared a polylactic acid dermal matrix to collagen for DFU closure. Healing was achieved in 9.3±2.9 weeks in the SDRM group (n=16) compared to 16.8±8.1 weeks using collagen (n=12).[30] This paper has recently been published in Wounds.[31]

The role of polylactic acid polymer as a temporary dressing for burns is well established, but its role as a dermal matrix or biodegradable scaffold for chronic wounds is just beginning to be studied. To date, our institution does not have first-hand experience with this product. Polymedics Innovations is planning to perform a prospective randomized trial of SDRM in DFUs, most likely involving more than 100 patients in multiple centers. This trial will likely start enrolling patients in the first or second quarter of 2024.

POWDERS AND GELS

Among the new synthetic products that have recently become available are powders and gels, which are composed of polymers that transform into a matrix within the wound bed. The appeal of these products compared to a more traditional matrix sheet is their ability to conform to irregular wound shapes. Regardless of whether these products are initially a powder or amino acid suspension, they can crosslink to form a hydrogel matrix that promotes healing while providing a protective barrier.

Altrazeal® (Uluru Inc.)

Of the many synthetics that are now available on the market, Atrazeal® (Uluru Inc., Addison, TX) is a promising new option due to its unique properties and clinical efficacy. Altrazeal® is a transforming powder dressing (TPD) composed of two biologically inert polymer particles, poly(2-hydroxyethyl methacrylate) and poly(2-hydroxypropyl methacrylate) (Fig. 5). Upon contact with moisture, these hydrophilic polymers irreversibly solidify from a powder into a protective hydrogel that retains the shape of the wound and provides moisture (Fig. 6).[32] When the polymers hydrate and aggregate, they orient as porous capillary channels, making the hydrogel extremely permeable and

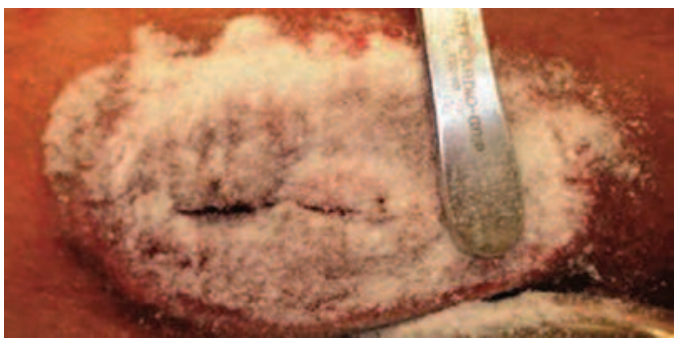

Figure 5. Transforming Powder Dressing (TPD) applied to chronic wound (Photo permission from Altrazeal).

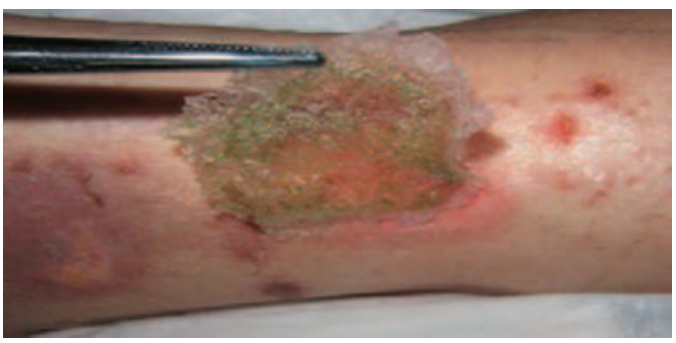

Figure 6. TPD hydrophilic polymers solidifying into conforming, protective hydrogel (Photo permission from Altrazeal).

allowing for wound exudate to easily travel to the surface of the wound bed. Additionally, the hydrogel dressing is 68% water, which increases its biocompatibility, since human skin is 72-74% water.[33]

Altrazeal® is currently indicated for surgical wounds, burns, and chronic wounds. An early case report on a patient with dystrophic epidermolysis bullosa showed significant pain reduction, fewer dressing changes, and improved healing after the application of TPD despite the intensely painful and hard-to-heal nature of these wounds.[34] Furthermore, several clinical studies and reports have documented its noninferiority and even superiority to SOC.

In a prospective, randomized, unblinded comparison by Assadian et al.,[33] patients who had been admitted to a single-center burn unit and required two skin graft donor sites were treated immediately after STSG application with TPD on one site and a silver-containing carboxymethylcellulose dressing (CMC-Ag) on the other. The endpoints were time to healing, daily pain scores, number of dressing changes, patient comfort, and willingness of the patient or physician to use the dressing in the future. The sites were assessed daily until 24 days post-application. Among the 19 patients included in the study, TPD was found to be non-inferior to CMC-Ag with respect to time to healing (14.2 vs. 13.2 days), but the pain scores were significantly lower and comfort was significantly higher in the TPD-treated sites compared to the CMC-Ag sites ($P<0.001$).[33]

A case series by Yu et al. published in 2022 evaluated the effect of TPD on hard-to-heal pressure ulcers (PU) in patients who failed to respond to SOC. They included stage 2-4 PUs and looked at the number of dressing changes, the time between changes, time until wound closure, and reported pain levels among patients treated with TPD. Among the 21 patients included in the series, all PUs achieved successful closure in an average of 13 days for stage 2, 41 days for stage 3 and 87 days for stage 4. The average number of dressing changes was 1, 4, and 6 for stage 2, 3 and 4 PUs, respectively. Additionally, reported pain scores decreased from 8 or 9 out of 10 to 1 or 2 by the first dressing change.[35]

In a retrospective, multicenter case series reported by Penny and Galiano,[32] the efficacy of TPD was assessed in stage 2–3 DFUs in 17 patients who had previously failed SOC therapy. TPD was applied and covered with a secondary dressing, and wounds were evaluated weekly with new applications as needed. The endpoints were days to healing, number of dressing changes, and days between changes. Of the 13 patients with stage 3 DFUs and 4 patients with stage 2 DFUs, all patients showed accelerated wound closure with a mean of 5.9 dressing changes and a mean healing time of 45.7 days. In this patient group, the authors concluded that the use of TPD directly led to a decrease in expected amputations.[32]

AC5 (Arch Therapeutics)

Distinct among the new synthetic options on the market, AC5 (Arch Therapeutics, Inc., Framingham, MA) is a self-assembling peptide matrix (SAPM) that is synthesized from naturally occurring amino acids. The SAPM facilitates hemostasis, serves as a barrier to prevent leaking from the wound bed, and promotes wound healing.[36] The peptide matrix is applied as a liquid. Upon contact with ions in the wound bed, it self-assembles into a bioabsorbable, nanofiber barrier network that resembles type I collagen and has a charge density similar to that of the extracellular matrix. This peptide scaffold decreases wound contamination and inflammation while concurrently promoting tissue growth and repair.[37] AC5 is currently FDA-approved for the management of partial- and full-thickness wounds, pressure ulcers, DLUs, VLUs, and surgical wounds. Several clinical reports have highlighted the efficacy of this SAPM for a range of wound types.

As a hemostatic agent alone, SAPM has been shown to be non-inferior, if not superior, to SOC in clinical studies. The time to hemostasis (TTH) with AC5 versus saline in a rat liver puncture model showed significantly faster hemostasis in the AC5-treated group (23.42 $\pm$ 9.25 s for the non-heparinized group and 22.5.0 $\pm$ 6.56 for the heparinized group) compared to saline (224.33 $\pm$ 74.0 s non-heparinized and 1060.0 $\pm$ 150.99 s heparinized). Equivalent hemostasis was noted in heparinized and non-heparinized AC5-treated animals.[38]

In 2018, Rahmani et al. published the results from a single-blind study evaluating the safety and efficacy of a SAPM on surgical wounds. Two sequential shave excisions were performed in 46 patients, 10 of whom were on antiplatelet therapy, and the lesions were randomized to either the SAPM or control treatment groups. The lesions were evaluated for TTH post-application, and at one week and 30 days for healing and safety profiles. Healing and safety were found to be equivalent in both groups, but TTH was significantly faster in the SAPM group compared to the control (median TTH 24.5 sec, range 7-165) vs 44 sec, range 10-387) and the median TTH was reduced by 41% ($p<0.001$). Of note, the median TTH was unchanged in the SAPM group regardless of antiplatelet therapy, but was more than doubled in patients on compared to off antiplatelets in the control group (90 vs 40 s, respectively).[39]

Several case reports have highlighted the efficacy of SAPM on chronic and hard-to-heal wounds compared to alternative products and SOC, and a decreased need for amputation. In a study by Treadwell and Nikolaychook,[40] 12 patients with intractable wounds, which had been present for at least 18 months and up to 5 years, were treated either weekly or bimonthly with SAPM while the wound area reduction was evaluated at 4 and 8 weeks. Among patients who were treated weekly, 75% had a greater than 50% wound area reduction by 4 weeks, and 88% had greater than 70% wound area reduction by 8 weeks. In patients who were treated every 2 weeks, half had a 50% wound area reduction at 4 weeks and greater than 60% by 8 weeks.[40]

A poster presented at SAWC Spring 2021 also showed the impressive efficacy of SAPM in a case of nonhealing malleolar ulcer that had been present for over 4 years in a patient with multiple vascular and autoimmune diseases. After three weekly applications of SAPM, the ulcer showed complete resolution.[41] Another poster presented at SAWC Fall 2022 also highlighted the role of SAPM in limb salvage. A patient with a 4-month recalcitrant malleolar wound after extensive debridement for necrotizing fasciitis underwent 4 weekly applications of SAPM and was found to have significantly decreased pain, along with granulation tissue formation and restoration of ankle function, and avoided amputation.[42]

In our experience with this product, we have seen some viscosity-related application issues. When using the product in the forefoot and on lateral

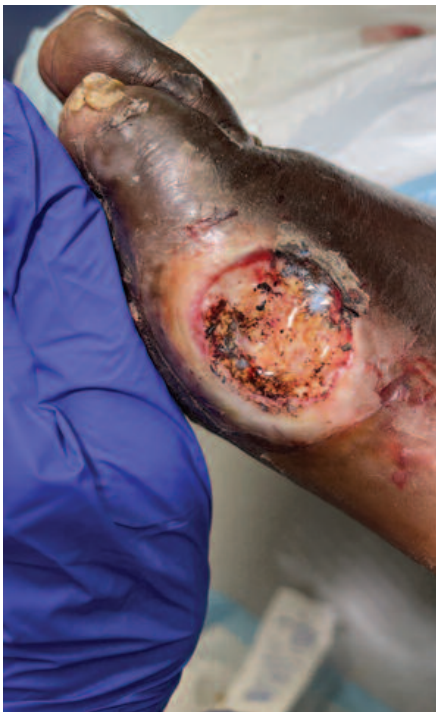

Figure 7. SAPM in lateral DFU after debridement.

lower-leg wounds, it has been difficult to keep this novel product on the wound (Fig. 7). However, this may not be an issue as this product is priced to be placed in the OR. In addition, as there is no current outpatient reimbursement for a flowable or liquid product, this will be limited to application in the OR for the foreseeable future.

G4Derm (Gel4Med Inc.)

G4Derm is a flowable synthetic extracellular matrix from Gel4Med Inc. (Allston, MA), a tissue regeneration company incubated out of The Harvard Innovation Lab. Its exact components remain proprietary. This self-assembling peptide hydrogel touts two major attributes: its manipulability within irregular wounds and its antimicrobial property. The flowable form is targeted for use in undermining or tunneling cutaneous wounds when the classic matrix sheet does not suffice. With the ever-growing number of multi-drug resistant organisms, a method for preventing and treating wound infections that does not depend on antibiotics is highly pertinent. The solution reportedly rids wounds of pathogens through disruption of the microbial membrane.

An abstract presented at a Wound Healing Society virtual meeting in 2021 demonstrated that this synthetic tissue scaffolding matrix was able to fully clear 10^6 colony forming units when applied to two common antibiotic-resistant strains of bacteria, methicillin-resistant Staphylococcus aureus and Pseudomonas aeruginosa, while not harming mesenchymal stem cells in vitro.[43] The matrix was tested in a controlled trial in both contaminated and noncontaminated diabetic wounds in a mouse model. The matrix therapy improved wound closure in noncontaminated wounds and accelerated granulation and re-epithelialization while decreasing leukocyte infiltration in contaminated wounds compared to controls.[44]

Although there have been limited reports on clinical work in humans so far, the promise of this flowable scaffolding matrix promoting infection-free tissue-healing without the use of antibiotics while also accessing tunneling wounds is intriguing. At the time of publication, this product had not yet received 501k pathway clearance from the FDA. The FDA has indicated that this therapy is similar to collagen-containing hydrogels that often sell for $7-10 per ounce. The product will probably undergo investigator-sponsored studies in 2023 and 2024, before potential prospective randomized trials in 2025.

ELECTROSPUN POLYMERS

This new market of synthetic products includes a subgroup of electrospun polymer matrices (EPM). Electrospinning technology has recently been developed and used for several biomedical applications, including pharmacologic drug delivery, tissue engineering, such as for rotator cuff or dural repairs, and the production of skin substitutes.[45] Electrospinning relies on a high electrical field between a metallic needle containing a polymeric solution and a ground collector. The synthetic polymers are then elongated and deposited as a matrix of nanofibers that is both durable and compliant. For advanced wound dressings, this permits the production of nanoscale composites that mimic native extracellular matrix in an efficient and reproducible manner. Additionally, these polymeric nanofibrous scaffolds can be fabricated with additives like growth factors or antimicrobials to further encourage healing.[46]

Restrata® (Acera)

Restrata® Wound Matrix (Acera Surgical Inc., St. Louis, MI) is a synthetic, resorbable, EPM that has emerged as an alternative to existing biologics. The nanofiber spun matrix mimics the architecture and porosity of human skin, promoting cell migration, differentiation, and neovascularization. The EPM is composed of two synthetic polymers, polyglactin 910 poly(lactic-co-glycolic acid) (PLGA) (10:90) and polydioxanone, which are electrospun together into 0.5mm-thick sheets (Fig. 8). Both polymers are naturally degraded by hydrolysis, so the matrix is fully resorbable and biocompatible. Due to its unique spun construction and composi-

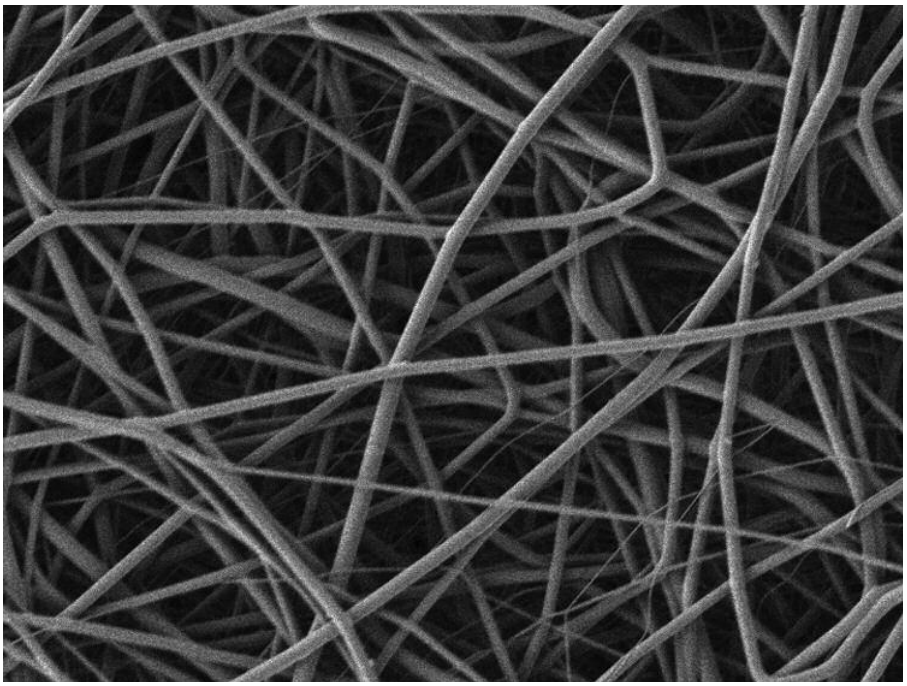

Figure 8. SEM of EPM (Photo permission of Restrata provided by Acera).

tion, the matrix is highly conformable, allowing for its application to a variety of wound shapes and sizes, and has a tensile strength comparable to that of human skin. Since the matrix is composed of slowly resorbable polymers, it also resists rapid enzymatic degradation by inflammatory cells as seen in chronic wound beds and requires fewer applications.[47] Hydrolysis into acidic components keeps the pH of the wound bed low to encourage healing.

Restrata® Wound Matrix was approved by the FDA in 2016 and is indicated in the treatment of partial- and full-thickness wounds, traumatic wounds, surgical wounds, VLUs, DFUs, pressure ulcers, and chronic wounds. Its overall efficacy in healing and its non-inferiority to other available biologics has been demonstrated in various clinical studies and reports.

In a pre-clinical comparative study by MacEwan et al., the rate and histopathological extent of partial-thickness wound-healing using an EPM versus a bi-layered xenograft was evaluated in a swine model. Compared to the control group, the average wound area was significantly smaller in the EPM-treated group at day 15 (7.7 $cm^2 \pm 0.9$ control vs. 3.8 $cm^2 \pm 0.8$ EPM) and day 30 (2.9 $cm^2 \pm 1.1$ control vs. 0.2 $cm^2 \pm 0.0$ EPM). Histopathological analysis of the wounds further showed superior healing rates in the EPM-treated group based on the observed degree of granulation tissue, mature collagen deposition, and earlier vascularization.[48]

In a retrospective study by Regulski and MacEwan, the overall efficacy of the EPM was evaluated in the treatment of chronic, nonhealing lower-extremity wounds. Eighty-two wounds (34 VLUs, 34 DFUs, and 14 other chronic wounds) were included in the study and by 12 weeks, complete wound closure was achieved in 85% of the wounds with a progressive and sustained decrease in wound area. Of note, among the treated VLUs, 90.9% achieved complete closure by 12 weeks.[49,50]

In March 2022, Abicht et al. published the results of a prospective, multi-center, clinical trial that evaluated the outcomes of using EPM for the treatment of DFUs over a 12-week period. Among the 24 DFUs included in the final analysis, 18 (75%) demonstrated complete wound closure by week 12 with an average reduction in wound surface area of 96% $\pm$ 10% and an average time to complete healing of 6.4 $\pm$ 2.5 weeks.[51]

Our experience in five patients has been as a single application in the OR for the treatment of DFUs or VLUs. In all but one case, the wound was either closed or ready for grafting at 4 weeks.

Phoenix Wound Matrix® (RenovoDerm)

Phoenix Wound Matrix® (RenovoDerm®, Dublin, OH) is another resorbable electrospun matrix of synthetic polymers that was designed to mimic the native extracellular matrix morphology, thus permitting cellular adhesion and proliferation. This EPM was approved by the FDA in 2018 for use in acute and chronic wounds as well as burns. Comprised of polyglycolic acid and poly(L-lactide-co-caprolactone), it naturally degrades by hydrolysis into a-hydroxy and fatty acids, which lower the pH and promote pro-regenerative cellular activity including angiogenesis.

The company's unpublished in vitro tests demonstrated a pH drop from 7.4 to 4.75 over one week as well as impressive cellular adhesion and proliferation. They reported a 40% decrease in matrix mass over 2 weeks when placed in isotonic PBS solution, which suggests that it has an appropriate lifespan to permit regrowth of native ECM. For their GLP porcine wound study, 2.0 cm full-thickness wounds were made and the EPM was applied to the wounds 48 hours later. It was left in place with a non-stick dressing for 31 days. Wounds completely re-epithelized during this time.[52]

Various posters at the Symposium on Advanced Wound Care presented the positive initial experiences of three different practitioners using EPM.[53] Garoufalis saw a >70% wound area reduction in 4 cases of hard-to-heal lower-extremity wounds within 4-5 weeks with an average of 3 applications. Schilling reported 4 patients with 5 recalcitrant DFUs that responded favorably to EPM. There was a 76% wound area reduction after just 3 weeks and complete wound healing occurred in 7.4 weeks. In 2023, Aviles described 4 cases in which EPM was used on a variety of wound types, such as necrotizing fasciitis, crush injuries and pressure ulcers, all of which achieved closure faster than expected. Another case series by the same author discussed the use of EPM in two limb-salvage cases with a total of 7 non-healing lower-extremity wounds. When NPWT was used in conjunction with EPM, these wounds healed in 5.6 weeks.[54]

Lambert et al. presented a prospective case series in which 38 patients with 50 difficult-to-heal wounds all received EPM over 12 weeks. Twelve wounds additionally received advanced therapies such as NPWT, hyperbaric oxygen and collagen dressings. As a result, the percent area reduction was 67.8% at 4 weeks and 80% at 8 weeks. Only 2 applications of EPM were required for 62% of the wounds. When followed to closure, the mean time to heal was 49 days for all wounds and 53.8 days for chronic wounds, which made up 70% of the total wounds.[55]

Currently, a pilot study (NCT04437537) is planned to examine the microbiome of chronic DFUs in 10 subjects prior to treatment with this EPM and one week following treatment. Ideally, this approach will be compared to other standard therapies by a randomized controlled study.[56]

Our early experience using EPM to treat 7 recalcitrant wounds of various etiologies demonstrated its ability to both kickstart healing in otherwise stagnant wounds and prevent seemingly inescapable deterioration. For example, one patient with an unstable Charcot foot and underlying osteomyelitis who refused both operative intervention and an offloading boot had a large plantar wound that was kept stable over 12 weeks (Fig. 9). Even after exposed necrotic bone was

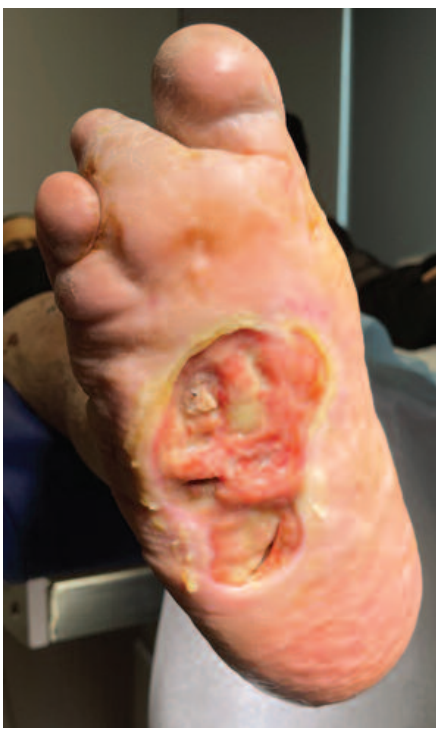

Figure 9. Large plantar wound on an unstable Charcot foot with underlying osteomyelitis kept stable with EPM.

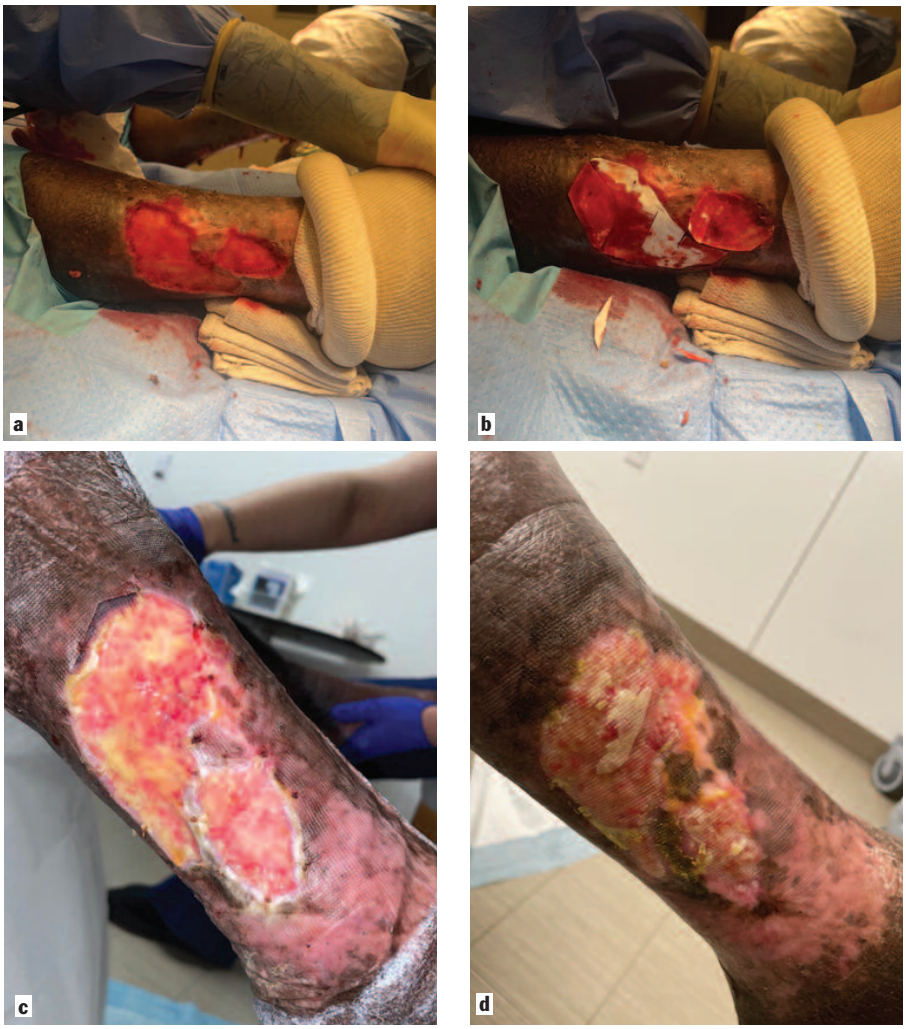

Figure 10. (a) Atypical lateral leg ulcer after operative debridement. (b) Placement of EPM in OR.(c) 1 week post-op. (d) 4 weeks post-op after weekly repeat applications in office .

resected, EPM helped expedite granulation tissue regrowth. Its effect on painful atypical ulcers was particularly notable as these ulcers have been resistant to innumerous therapies. Application of EPM to 3 atypical leg ulcers helped reduce both wound size and pain. The 2 ulcers in the right leg reduced in size by 33% and 60% after 12 applications, respectively, and pain (as reported on a VAS) reduced from 9 to 4. The larger left leg ulcer reduced by 28% after only 6 applications and pain lessened from 10 to 6 (Fig. 10). Although our experience against terrible odds with these incredibly hard-to-heal ulcers has been encouraging, further studies are needed to validate these anecdotal findings.

Spincare ™ (Nanomedic Technologies Ltd.)

Spincare™ is a nanofibrous extracellular matrix applied with a handheld electrospinning device made by Nanomedic Technologies, Ltd. (Lod, Israel). It still requires FDA review, and thus is not currently available in the U.S. The portable device prints the proprietary polymer solution directly on the patient, where it acts as a temporary skin-substitute that is indicated for partial-thickness burns and wounds. The disposable solution ampules can be modified with various additives such as antibacterial agents, collagen, and adhesive materials, as well as the patient's own harvested cells.

Haik et al. trialed four different electrospun polymer formulations on partial-thickness wounds in a porcine model compared to a standard dressing. They found that all wounds healed within the same time but the eletrospun matrix offered advantages in terms of its ability to be applied from a distance and its excellent surface topography.[57] Dong et al. performed in vivo studies on rats using an electrospun antibacterial nanofibrous membrane and observed accelerated wound healing, better exudate management and reduction of the inflammatory response.[58]

Various case reports have so far ascertained its utility for burn wounds in humans.[59] Partial-thickness burns on challenging anatomical areas to apply dressings such as the hand or shoulder were adequately covered by the matrix, thus avoiding the need for numerous dressing changes, and completely healed by day 14. Another 10% TBSA burn with complex body contour over the neck, shoulder and torso healed by day 7. The transparency of the matrix allows for clinical re-assessment, which was shown to be greatly advantageous when a presumed 2nd degree burn covering 18% TBSA turned out to be a 3rd degree burn and required a change in treatment approach. Additionally, the matrix works well on skin graft donor sites, where it acts as a protectant layer that lasts until fully re-epithelized.

Schulz et al. trialed the new SpinCare™ system on 10 patients with superficial to partial-thickness wounds and found good healing and improved aesthetic outcomes. After discussing the initial learning curve faced using the device, they proposed a 3-day algorithm of care for its use after enzymatic debridement.[60] Agathangelou et al. also had promising results when using in situ electrospun nanofiber scaffolds on 12 patients with hard-to-heal wounds that had been previously treated with other advanced wound care products. All patients healed within 3-12 weeks, with reduced exudate levels and improved periwound skin and pain levels.[61]

The take-home advantages of this technology are that it creates a customizable epidermal layer for wound coverage that adheres well, reduces dressing changes, permits visualization of the healing process and is conformable for patients.

ELEMENTAL ENGINEERED MATRICES

Various metal ions, which have been found to have pro-regenerative or antimicrobial properties, can be added to tissue-engineered and bioactive glass matrices for wound-healing purposes.[62,63] In an age of increasing bacterial resistance, "ion doping," using metals such as silver, zinc, titanium, gallium and others, has become an increasingly popular means for managing biofilms. Silver is a well-known antimicrobial agent that has been added to synthetic extracellular

matrix scaffolds to keep microbes at bay.[64] In addition to potential antibacterial properties, boron has been shown to regulate the release of collagen, proteoglycans and proteins while encouraging keratinocyte migration.[65,66] These bioactive metal elements can be incorporated into new synthetic skin-substitutes to theoretically accelerate wound repair.

Microlyte® (Imbed Biosciences)

Microlyte® Matrix (Imbed Biosciences, Middleton, WI) is a tissue-engineered matrix that first became available on the market in 2021. It has shown measurable, if not superior, success compared to many other available wound products. Microlyte® is a silver-delivering bioabsorbable polymer matrix (BPMAg).[67] It consists of a polyelectrolyte multilayer nanofilm scaffold that acts as a template for tissue granulation and a coating of polyvinyl acetate and ionic and metallic silver that confers hydrophilic and bioresorbable properties. The biodegradable matrix conforms to the tissue and promotes moisture trapping.[68] The added low-dose silver also provides antimicrobial activity as seen with traditional silver-coated dressings but, due to the significantly lower silver dose, adverse effects associated with these dressings, such as inflammation, metal toxicity, and tissue staining, have not been observed.[69] BPMAg has been shown to be efficacious in healing a variety of wound types and is currently indicated for debrided tissues, graft sites, and full-thickness burns as well as for preventing post-operative wound infections in high-risk patients (Fig. 11).[70]

BPMAg has also shown significant promise in treating chronic wounds. An open-label, prospective, pilot study examined the efficacy of BPMAg in treating recalcitrant wounds that had been present for an average of 40 weeks. BPMAg was applied 1-3 times a week in 32 patients and the wounds were evaluated weekly for improvement and average closure. By week 3, 72% of the wounds had improved, with an average wound area reduction of 66%, and by week 12, 91% of all wounds had improved or healed completely with an average reduction of 73%. Additionally, patients reported virtually no pain with initial and subsequent applications.[68] Another pilot study using BPMAg for treatment of chronic VLU demonstrated that 9 of 10 patients with VLUs that had been refractory to SOC for over 6 months showed significant improvement, with an average 48% closure by 4 weeks.[71]

There have been several reports on its ability to help heal contaminated wounds burdened with biofilms. In a case series presented by Beatty and Jones, three recalcitrant leg wounds with significant biofilm buildup and exudate were treated either weekly or biweekly with BPMAg after wound cleansing. In all of these wounds, significant progress toward healing was observed and no infections were noted, highlighting the ability of the easy-to-use dressing to suppress biofilm buildup and act as a template for healing.[72]

We tried BPMAg on 30 patients with chronic lower-extremity wounds by applying the matrix 1-3x per week for 4 weeks; we observed a mean wound area reduction of 72% as well as reductions in pain and drainage (Fig. 12). Notably, 20% of our patients, all of whom had a significant dermal component for their wound, did not respond significantly, suggesting that the use of BPMAg may be better suited for more superficial wounds and is a nice last-stage treatment until fully re-epithelialized. Overall, the ease of application and reduction in drainage made this dressing very attractive. Due to pricing issues, this product can no longer be used in the same manner as in our experience. It now requires pre-authorization and approval is granted for no more than weekly applications. Therefore, we do not currently use this product.

Mirragen® Bioactive Glass (Engineered Tissue Solutions)

Originally implemented in bone regeneration, engineered bioactive glass has more recently been highlighted as an advantageous skin-substitute that promotes angiogenesis, prevents infection and facilitates tissue repair and healing.[73] Mirragen® (Advanced Wound Matrix; Engineered Tissue Solutions, North Rolla, MO) is currently the only bioactive glass skin-substitute that has been

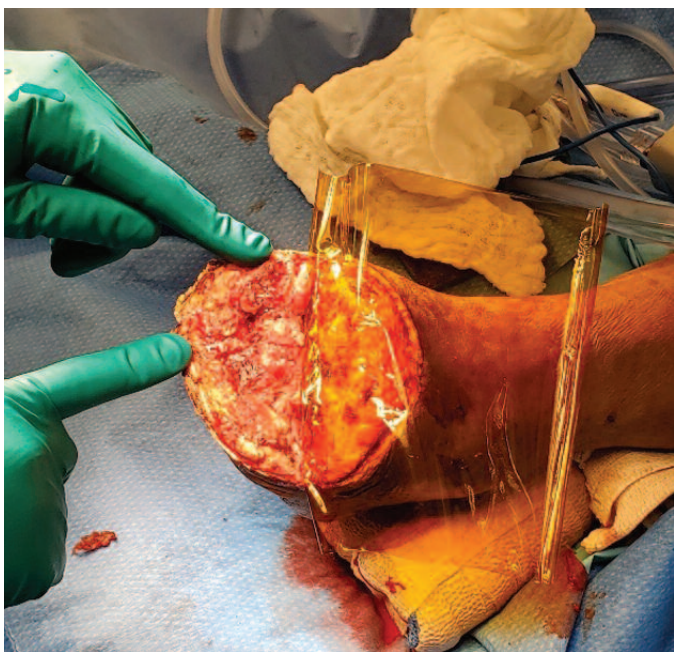

Figure 11. BPMAg applied to high-risk trans-metatarsal amputation.

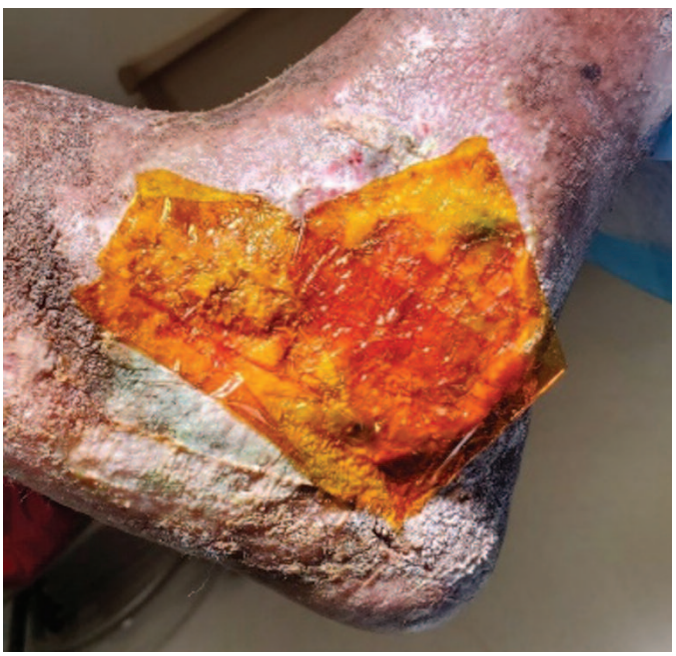

Figure 12. BPMAg applied to chronic medial ankle wound.

FDA-approved for wound-healing on the market. It is a boron-based glass fibrous matrix (BBGFM) that acts as a scaffold for tissue engineering by mimicking the ECM of human skin. Its specific design allows it to absorb up to 400% of its weight in exudate. The matrix also contains biocompatible calcium, magnesium, and phosphorous ions which are released upon exposure to fluid and absorbed by the surrounding tissue.[74] Once absorbed, the ions stimulate a range of cellular processes including cell migration, angiogenesis, and fibroblast proliferation, as well as antimicrobial activity. The matrix is biocompatible and resorbable, nonimmunogenic, and conforms to the unique shape of the wound.[75]

Mirragen® is currently indicated for partial- and full-thickness wounds, pressure ulcers, VLUs, DFUs, vascular ulcers, surgical and donor site wounds, trauma wounds, and dehisced and draining wounds.[76] Despite its more recent emergence in the wound care market, several trials and studies have documented its superiority to SOC and alternative synthetics.

In a study by Jung, BBGFM was evaluated after application to full- and partial-thickness wounds in a porcine wound-healing model against two other commercial collagen and polymer fiber dressings. At the conclusion of the study, BBGFM was found to have superior rates of wound closure, a higher percentage of epithelialized wound surface, and a lower level of inflammation compared to the other dressings.[77]

In a case series by Cole, weekly applications of BBGFM were performed on three patients with chronic, hard-to-heal wounds of varying etiology after saline cleansing and debridement. All 3 cases showed evidence of complete wound-healing in less than 4 weeks. The author noted that, throughout the healing process, no evidence of secondary dressing saturation or peri-wound tissue maceration was observed, and the healing properties of the matrix supported repair and regeneration of soft tissue defects in all 3 cases.[78]

A multicenter single-blind randomized control trial published in 2021 on the effect of a resorbable BBGFM in the treatment of DFUs showed significantly improved healing rates with the addition of BBGFM compared to SOC alone. In the trial, the proportion of full-thickness, non-infected, non-ischemic healed wounds as well as the percent area reduction and changes in monofilament testing were evaluated at 12 weeks in 20 patients. By week 12, 70% of DFUs in the treatment group had healed compared to only 25% in the control group (P=0.006). Additionally, the mean wound area reduction was 79% versus 37% (P=0.027), and the mean change in the neuropathy score was 2 versus -0.6 in the treatment versus control groups, respectively (P=0.008).[79]

We used BBGFM on 8 patients and 11 large or challenging chronic wounds, either DFUs or VLUs, over 4-8 weeks. Overall, the mean wound area reduction was 43% after an average of 4.4 applications (Fig. 13). By week 8, three patients with DFUs (27%) had completely healed and there was a greater percentage wound area reduction in DFUs (63%) than in VLUs (26%) (Fig. 14). Many of these wounds had been refractory to other treatments, including cellular or tissue-based therapies. Although healing rates were higher for DFUs, the effect of BBGFM on incredibly stagnant VLUs was equally as impressive. BBGFM appeared to improve wound healing in our patients with challenging chronic wounds without any negative outcomes.

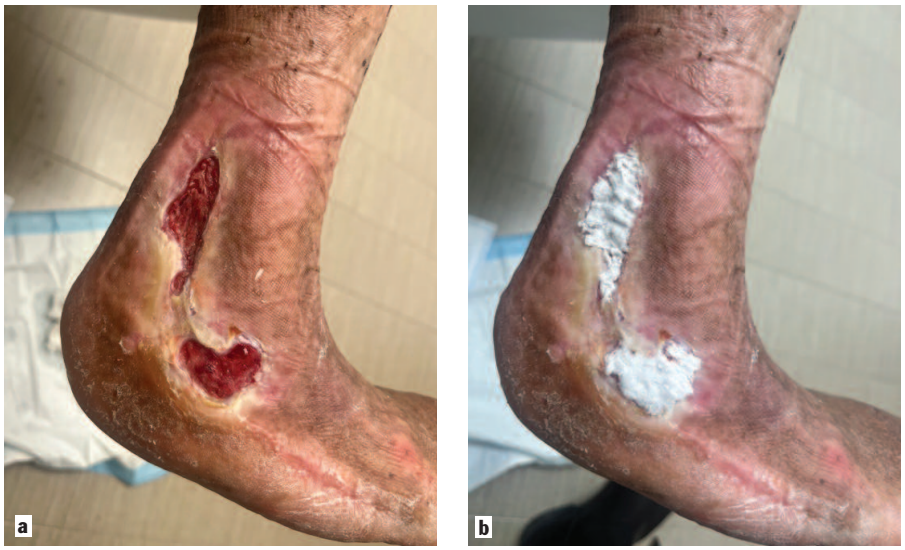

Figure 13. BBGFM applied to chronic VLU, helping to reduce the wound size and improve periwound health.

CONCLUSION

Synthetic dermal matrices are new to the wound care market and, although they have not yet been formally sorted and categorized according to their various properties, they have shown promise

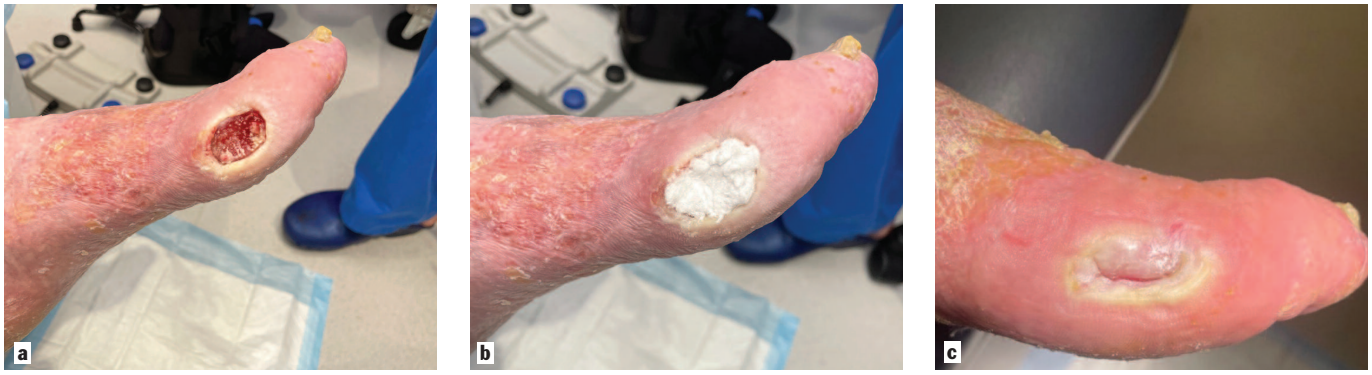

Figure 14. (a) Diabetic patient requiring revascularization and debridement of the first metatarsophalangeal (MTP) joint for acute osteomyelitis. (b) BBGFM applied to wound. (c) 1 month after weekly applications.

as a whole. Most interestingly, these products make one consider the various qualities of an extracellular matrix. These materials may seem inert, but they are not. Although none of these materials add proteoglycans or glycosaminoglycans, or deliver growth factors or living cells to a wound, they help to close wounds in an innovative fashion.

In general, based on our experiences and those of other practitioners, the overall results using synthetic matrices have been positive. In most cases, their application is very easy, they have a very long shelf-life and they tend to modulate towards a robust granulation tissue. Most of these products require a secondary dressing such as a nonstick layer and then potentially a moderately absorbing layer over that, which is fairly standard for all cellular, acellular and synthetic matrix products. However, most of the reports on these synthetic products to date have just been case series. More head-to-head comparisons of these wound-modulating products with other biologic products are probably necessary, particularly since we have started turning to these products for use in patients for whom advanced biologics have been ineffective.

The cost of these products appears to be somewhat arbitrary. Any product certainly has intrinsic research, manufacturing and development costs. However, in most cases, the sourcing of materials for these products is not very expensive. The United States healthcare market and CMS reimbursement policies push many of these products to be sold at costs that are significantly greater than they need to be. In some cases, the cost of the products was initially significantly lower, but then the costs were artificially elevated to conform to our U.S. healthcare reimbursement system. This increase has occurred despite any evidence that these products offer a significant cost advantage, although for many of these synthetic matrix options, their large sheet size and longer dwell time have some clear advantages over traditional engineered biologics.

There may be no single ideal regenerative wound matrix for use in all cases because patient factors will always be a major consideration. However, synthetics are attractive given they can be quite sophisticated and purposeful. Any pH-lowering and antimicrobial activity are likely to be universally beneficial for large chronic wounds. The addition of these properties to durable but biodegradable scaffolds makes them strong contenders in the wound care market. STI

AUTHORS' DISCLOSURES

The authors declare that there are no conflicts of interest.

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