The Evidence for Antimicrobial and Hard to Infect Regenerative Matrices

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ABSTRACT

Preparation of the wound bed is a key step in the use of cell- and tissue-based therapy (CTP). In particular, good pre-application debridement is an essential component of CTP. However, there are many situations in which the wound bed is not adequately debrided, including trauma, burn, and in cases of chronic wounds with significant biofilm. In the setting of inadequate wound bed preparation, the use of a CTP that has either added or intrinsic antimicrobial properties is attractive. Some CTPs include added antimicrobial agents such as PHMB or silver, while others have intrinsic antimicrobial components, such as Omega 3 fatty acids. In addition, some wound-covering dressings are completely synthetic, and therefore simply do not become infected. A full understanding of the basic science and clinical data supporting the use of these therapies is important for the advanced wound care practitioner.

INTRODUCTION

When a chronic wound has not reduced in size by 40-50% after four weeks of appropriate care, many clinicians in the United States consider using cell- and tissue-based therapy (CTP) as an adjunct to promote wound healing, even though most studies show closure rates of only 60-70% after 12 to 16 weeks of application.[1] One reason that these rates are not higher is thought to be inadequate wound bed preparation.[2] The ongoing prevalence of biofilm and planktonic bacteria within the chronic wound and contaminated acute wound makes the application of CTP more likely to fail. Therefore, serial debridement in conjunction with the use of topical antimicrobials remains the backbone of wound bed preparation prior to the application of CTP.

To theoretically enhance the likelihood that use of a CTP will achieve wound closure, antimicrobial agents have been added to some products to enhance their resistance to a hostile microbial environment, including Puraply® AM (Organogenesis, Canton, MA) and Primatrix® AG (Integra, Princeton, NJ). Other xenograft products appear to simply be intrinsically more resistant to bacteria, such as the Kerecis® Omega3 Wound (Kerecis, Isafjordur, Iceland). There are also some non-biologic "dressings" which, while having phenotypic responses similar to those of CTPs, have very different mechanisms of action; these include the NovoSorb® BTM (PolyNovo, Port Melbourne, Victoria, AU) and MicroLyte® Matrix (Imbed Biosciences, Fitchburg, WI).

In this review, for each of these products, we will discuss its currently understood mechanism of action, the clinical data to support its usage, our own experience with the product, the best dosing or application strategy, and possible algorithms of care for how best to use the product. Finally, we will attempt to compare the quality of the data, the time of therapy, and the cost of all of these products.

PORCINE COLLAGEN WITH PHMB (PURAPLY® AM; ORGANOGENESIS) (PCPHMB)

Mechanism of Action

PHMB is a bactericidal agent that exhibits differential access to bacterial and mammalian cellular DNA. This characteristic allows it to selectively bind to and condense bacterial chromosomes. To date, acquired resistance to PHMB has not been reported, and it appears that this mechanism of selective chromosome condensation provides an unanticipated paradigm for antimicrobial action that may not succumb to resistance.[3] PHMB is added to intestinal submucosa to create an antimicrobial device. While the makers of PCPHMB call it a "native collagen", this term has almost no scientific meaning. In general, the company that distributes this product is very opaque about the origin of the collagen, to the point that their senior sales force does not know its origin. Since it is well known that collagen is preserved across species, its source may not make a difference.

PCPHMB is a type I porcine-derived collagen matrix coated with 0.1% PHMB. It is a Food and Drug Administration (FDA) Class II 510(k) cleared medical device (#K051647) that is intended for the management of wounds as an "effective barrier to resist microbial colonization within the dressing and reduce microbes penetrating through the dressing". It is not indicated for the treatment of infected wounds, nor for use as a drug-delivery system. PCPHMB is the only dressing available in the United States that combines a collagen matrix and PHMB.

In a well-recognized in vitro model, the antibacterial effect of PCPHMB was evaluated using MRSA USA300.[4] In this study, using a modified Kirby-Bauer method, the various products were exposed to low and high levels of the inoculum MRSA (USA300) to simulate wounds with low and high levels of colonization, respectively. To determine how long the material was able to suppress bacterial growth, the antimicrobial activities of the materials were evaluated by incubating the test agent in sterile PBS at 37°C for up to 10 days. After 10 days, the effectiveness was checked by measuring the area of the zone of inhibition. For PCPHMB, this in vitro antimicrobial effect persisted for 10 days. The authors used a standard human dermal fibroblast (HDF) assay, and measured cell growth over an incubation period with media conditioned with the test material. As a result, the PCPHMB was non-cytotoxic, with no detrimental effects *in vitro* on fibroblast proliferation or viability.[4]

This in vitro work was augmented by testing in an in vivo animal model. Twenty-one standardized wounds were created in 6 female swine, which were then inoculated with a fresh culture of methicillin-resistant *S. aureus* (USA300). In this elegant model, biopsies were performed on days 4, 8 and 11. PCPHMB was noted to reduce MRSA by 99% (second only to much more caustic antimicrobial dressings), while significantly enhancing fibroblast viability and wound closure histology.[4]

Clinical data

A prospective registry of PCPHMB has been reported in which no actual bacterial or antibiotic stewardship data were collected.[5] As in most studies, improved wound closure was considered a surrogate for the downregulation of planktonic and biofilm-protected bacteria. Sixty-three patients with hard-to-heal wounds were considered, and included venous ulcers (28.6%), trauma and lacerations (22.2%), postsurgical open wounds (15.9%), pressure injuries (12.7%), and diabetic ulcers (9.5%). The median baseline wound area was 6.5 cm^2 and the mean wound duration at baseline was 4 months. Of the 63 wounds, 43 (68.3%) achieved complete wound closure; 41 of these 43 (95.3%) closed after PCMP treatment and the remaining 2 of 43 (4.7%) closed after bridging to other modalities and surgical closure. The mean time to closure for PCMP wounds was 5.0 weeks.[5]

Our own experience

While we have access to this product, due to its cost we tend not to use it very much. Therefore, we will discuss the best dosing and application strategy in terms of our colleagues' published data.

Best dosing or application strategy

Oropallo published a single-author, single-center prospective case series of PCPHMB patients who underwent an initial sharp or mechanical debridement.[6] Patients received standard wound care plus PCPHMB applications at week 0 and then weekly up to week 12 at the investigator's discretion. She treated 41 wounds, including pressure ulcers (44%), surgical wounds (22%), venous ulcers (12%), diabetic ulcers (10%), and some other type (12%). The median (interquartile range) baseline wound area was 7.2 (14.9) cm^2, and the mean wound duration was 103 weeks. Of the 41 wounds, 73% demonstrated a reduction in wound area at 12 weeks, and 37% achieved complete wound closure, with a mean time to complete closure of 6.7 weeks.

Oropallo used a dosing frequency of application in place for a minimum of 1 week and a maximum of 3 weeks. The product was applied with Steri-Strips™ (3M, Saint Paul, MN) and fixed with a non-adherent dressing followed by a foam dressing.

As is often the case in such studies, the patients had very hard-to-heal wounds, as evidenced by an open wound duration of 2 years or greater. However, the mean number of applications of the product was 8, which raises the question of whether the product is truly cost effective. On the other hand, these are clearly very difficult-to-heal wounds. Again, as in most studies, the wounds that healed required significantly fewer applications of product. For wounds that achieved complete closure, the mean (SD) time to closure was 6.7 (3.0) weeks. Of the 41 wounds, 30 (73.2%) demonstrated an overall reduction in wound area over the 12-week study, and 15/41 (36.6%) achieved complete wound closure. When the wounds were considered according to wound type, 7 of 18 (38.9%) pressure ulcers, 5 of 9 (55.6%) surgical wounds, 1 of 1 (100%) trauma wounds, 1 of 4 (25%) diabetic foot ulcers, and 1 of 5 (20%) venous leg ulcers achieved complete closure. Since it is reasonable to expect both post-op wounds and trauma wounds to close, since they are actually acute wounds, it would appear that this product is best used to treat pressure ulcers, for which the closure rate is far above the expected rate. One study looking specifically at using a "native collagen", basically the same "native collagen" found in PCPHMB, showed that in a control group of 130 adults with stage III or stage IV pressure ulcers, while those who received standard of care had a 29% chance of complete healing over 12 weeks, those who were treated with porcine submucosa had a 40% chance of healing. In the same study, the percentage of patients who experienced a 90% reduction in the ulcer area was 55% chance in patients treated with a collagen product but only 38% in those who received standard of care.[6]

Possible algorithms of care

This antimicrobial ECM has been shown to be widely applicable to numerous types of wounds, and appears to be particularly beneficial in the treatment of pressure ulcers. The reports by Oropallo[7] and Bain et al.[5] both include a very diverse wound population, which raises the question of whether all wounds should be treated with this agent. In general, the answer is probably, "No". However, as a wound bed-preparation product, we can discuss the use of reducing bacteria and improving granulation tissue prior to the application of a definitive closure solution.

ACELLULAR FETAL BOVINE DERMIS WITH SILVER (PRIMATRIX® AG; INTEGRA) (FBDAG)

Mechanism of Action

Silver kills bacteria possibly by various mechanisms. Recently, it has been elucidated that silver accelerates the dynamics of a protein in *E. coli*, which ultimately causes the nucleus to "burn out".[8] In addition, the researchers observed that silver ions caused paired strands of DNA in the bacteria to separate, and the binding between the protein and DNA to weaken. The more rapid motion of this protein is related to the protein being unbound from DNA. At least in *E. coli*, this leads to cell death.

FBDAG has several mechanisms of action. For example, it offers a template within which native cells can grow, actually creating a true dermis, and thus it is indicated for the regeneration of dermis. In addition, it can attract circulating pluripotent stem cells.[9] FBDAG is a single-application fetal bovine dermal matrix in which the natural structure of the collagen is preserved. Fetal bovine collagen without silver has been widely studied with very good outcomes. It was recently studied for use in patients with diabetic foot ulcers, and provided outcomes superior to those with the standard of care.[10] This product has also been studied in the setting of venous leg ulcer, and has been extensively used in multimodal wounds. It is usually administered as a single application.

FBDAG consists of FBD with up to an average of 165 μg of silver per square cm. The acellular collagen matrix derived from FBD is rich in type III collagen, which is active in developing and healing tissues and has a 34-month shelf-life at room temperature. It is indicated for the management of both partial- and full-thickness wounds. The senior author has reviewed internal documents provided by the manufacturer (Integra Lifesciences, Princeton, NJ) that support the following points: 1) in routine antimicrobial panel testing, FBDAG is effective for killing microorganisms, 2) a preclinical study showed that, even with ionic silver embedded in the scaffold, it is not toxic to local tissue, and 3) an in vitro animal study demonstrated that FBDAG is effective in preventing biofilm formation by *S. aureus*, *Pseudomonas* and MRSA. However, none of these studies have been peer reviewed and they are not in the public domain.

Rennert and co-workers evaluated FBD in 2013. They analyzed the cellular response to FBD in vivo, and determined this tissue's ability to exhibit dermal regeneration. In this study, FBD was implanted subcutaneously in the back of a mouse. At multiple time points up to 4 weeks, tissue samples were harvested and examined by histology, immunohistochemistry and flow cytometry. The results revealed that tissue engraftment began with infiltration by inflammatory cells, followed by mesenchymal cells recruitment, which eventually lead to functional vascular beds. Immunohistochemistry demonstrated that the wound contained FBD for up to 4 weeks. The bovine collagen underwent significant remodeling and cellular repopulation. Standard H and E staining showed that the material that remained in the wound approximated normal healthy dermis. The authors concluded that FBD implants undergo in vivo remodeling.[9]

There is almost no basic science or clinical data to support the use of FBDAG. A large, 304-subject trial in the UK showed no significant differences in either primary or secondary endpoints between the use of antimicrobial silver-donating dressings and a control group of low-adherent dressings. In addition, financial modeling showed that antimicrobial silver dressings were not cost-effective.[11] In a previously discussed paper, this product underperformed compared to a PHMB product when assessed in terms of a reduction in *S. aureus*. The low level of silver and the mechanism of delivery reduce its efficacy against *S. aureus*. Overall, it is important to remember that the product is indicated to reduce bacteria in the product, but not actually to treat the wound.[4]

Our own experience

We have used this product electively when the patient has not responded well to FBD. In summary, in some cases when FBD without silver is placed on a wound, the FBD goes away very quickly. We consider this to be sacrificial, and in this setting we will debride and reapply FBDAG (Fig. 1). While such cases are rather infrequent, we have been happy with the outcomes.

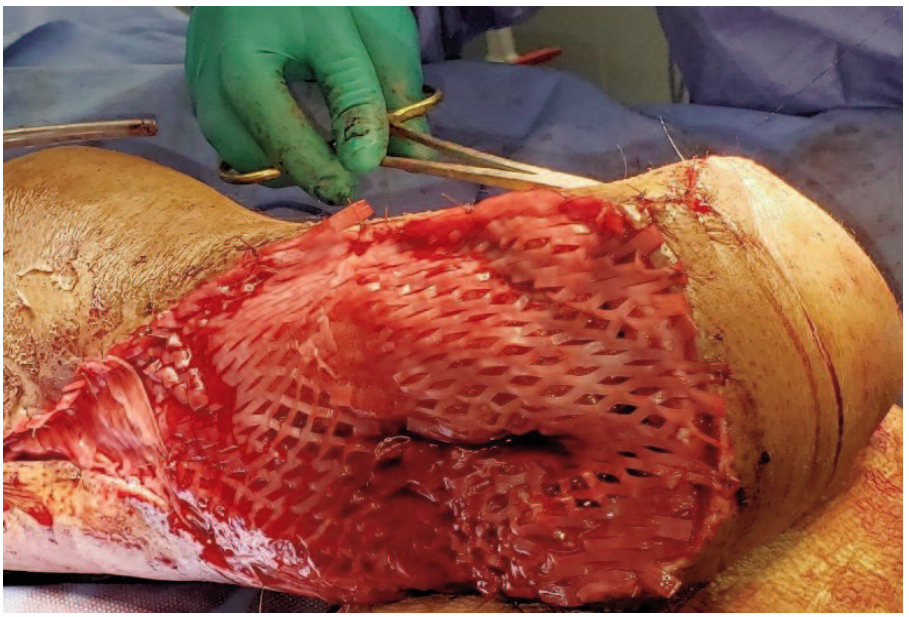

Figure 1. Fetal bovine dermis with silver being applied to a heel wound. Since this product can oxidize after application, it may appear very dark (black) in follow-up. When the wound is greater than 40 cm², we always combine this product with negative pressure wound therapy.

Best dosing or application strategy

Our center has used this product only as a rescue graft after failed FBD. The lack of prospective evidence has hampered its use at our center. This product is usually applied as a single application, which is usually adequate to enhance dermal regeneration. The product is applied in the operating room after thorough debridement and sutured in place with 4-0 Chromic suture. A non-stick contact layer is placed in addition to a bolster. An appropriate secondary dressing is then applied. In general, the dressing is then removed and the wound inspected at weekly office visits.

Possible algorithms of care

One theoretical advantage of the product is that it may be placed in a heavily colonized field and can only require a single use. Although we would advocate wide excisional debridement prior to application, this single-application product with which we are attempting to regenerate dermis may stand up better to the hostile environment of a contaminated wound. In our experience, the dermal construct created by FBD is very robust and holds up well over time.

ACELLULAR INTACT FISH SKIN (KERECIS® OMEGA3 WOUND, KERECIS) (AFS)

This North Atlantic cod skin-derived extracellular matrix is the only cell- or tissue-based therapy that retains its native fats. The antimicrobial mechanism of action appears to involve the presence of Omega-3 fatty acids. Researchers have shown that docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the two major Omega-3 polyunsaturated fatty acids (ω-3 PUFAs) with antimicrobial properties. In one study, the ω-3 PUFAs EPA and DHA showed antimicrobial and anti-biofilm activity in vitro against *S. aureus*, *S. epidermidis*, and *P. aeruginosa*, as well as against multi-drug-resistant *S. aureus* and CoNS strains isolated from patients undergoing treatment for periprosthetic joint infections (PJI). Higher concentrations of the fatty acids killed planktonic cells and inhibited biofilm formation. Although both substances showed antimicrobial activity, EPA showed better results than DHA. In addition, when applied to human gingival fibroblasts in vitro, EPA and DHA showed a possible protective effect in cell culture.[12]

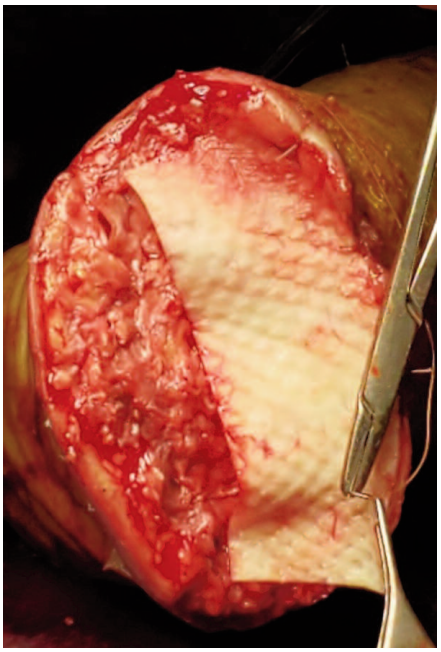

Figure 2. Acellular fish skin being applied in the OR.

In a direct assessment of AFS using the classic two-chamber *S. aureus* model, AFS was placed between the insert units and injected with broth. The upper chamber was then seeded with *S. aureus* (5000 cfu in 200 µL TSB) strain ATCC 25923. The unit was incubated at 37°C until the lower chamber was contaminated. In the two-chamber assay, the fish skin graft performed as a bacterial barrier for close to 60 hours, compared to 5–45 hours for human amnion/chorion membrane products and several collagen matrix products.[13] Spiking (>10%) the fish skin with more Omega-3 fatty acids enhanced its bacterial barrier function by roughly 80%.[13] A mouse burn-infection model was used to further investigate this effect of AFS.[14] In this model, mice were burned for 30 sec with brass blocks to create a 3rd-degree burn. The wounds were infected 5 minutes post-burn with 400-480 x 10^6 of *P. mirabilis* strain ATCC51393. If the AFS was applied to the burn wound prior to inoculation, there was no sign of infection at one week, and closure was observed at 2 weeks. Furthermore, in mice treated with AFS, there was 100% survival, while animals that were not treated with AFS showed 50% mortality.[14]

Clinical data

In a retrospective review, 54 non-healing wounds were treated with AFS for four weeks with a median of 2 applications. Interestingly, there was an unexpected 38% reduction in the use of antibiotics.[15] In addition, there was an 87% decrease in wound area in non-healing wounds that were treated with fish skin grafts. Interestingly, none of the wounds became worse over the 4-week treatment with AFS. According to wound types, 83% of the 10 surgical or traumatic wounds improved, as did 92% of the 25 venous leg ulcers, 71% of the 5 arterial ulcers, and 87% of the diabetic foot ulcers.

A prospective, randomized, French trial evaluated AFS for the closure of split-thickness skin-graft (STSG) donor sites in 21 cancer patients who were operated on for radial forearm free flap reconstruction for head and neck wounds.[16] The healing time was halved when AFS was used, from an average of 68 to 32 days. However, for our purposes, AFS reduced the infection rate from 60% to 0% ($p=0.0039$). The authors noted that the "infection rate" at the STSG donor site is much higher than what we would usually expect. AFS has been the subject of multiple prospective studies which have not looked specifically at infection but have looked at clinical efficacy in acute wounds and diabetic foot ulcers, and of retrospective studies in venous leg ulcers, all of which show significant clinical efficacy but do not address antimicrobial activity.[17-20]

Our own experience

This product actually requires very little preparation of the wound bed and handles well in a poorly prepared wound bed.[20] We have used this material in venous leg ulcers with very little preparation of the wound bed. In the outpatient setting, we use this actively for diabetic foot ulcers (Fig. 2). The patient undergoes sharp debridement of surrounding tissue and the product is applied directly to the wound bed. This often requires a weekly application, and in our experience a median of 5 applications is necessary for patients who experience wound-healing. If the patient has not had a significant reduction in area by the 4th application, application should be discontinued. We have used this product extensively in the operating room as well for in larger reconstructions and note that grafting can be achieved soon after application. In some cases, skin graft can be done as early as 1 week. We are very unconcerned about placing this product in

patients with clear-cut bacterial contamination.

Best dosing or application strategy

In the outpatient setting, a median of approximately 5 applications are needed to close the wound. This has recently been shown in a prospective randomized trial in diabetic foot ulcer as well as in a venous leg ulcer trial. In our own experience, the wound-healing trajectory in the outpatient setting is best taken complete closure with the product. In other words in the chronic wound the closure rate appears to be dependent upon ongoing application of the product.[20] Aggressive wound bed preparation is not always necessary for this product despite the manufacturer's instructions for use.

In the inpatient setting, this product can be affixed after wide surgical debridement. It facilitates early skin grafting and closure, sometimes as soon as one week later. This is a very different application strategy than in the outpatient setting. AFS's bacterial resistance makes it ideal for use with heavily contaminated wounds and wounds with a significant inflammatory basis such as hidradenitis suppurativa, pyoderma gangrenosum, and burns.

Possible algorithms of care

Diabetic foot ulcers in the outpatient setting and venous leg ulcers in the outpatient setting can benefit from this product with appropriate application. In the setting of diabetic foot ulcers, comprehensive offloading is mandatory, and in the setting of venous leg ulcers, appropriate venous reconstruction and multilayer compression are needed. For the deeper diabetic foot ulcer with bony resection, and with the patient in the operating room, we have applied this product immediately postoperatively in conjunction with negative pressure wound therapy to help facilitate early granulation tissue and then move on to re-application of AFS on a weekly or biweekly basis in the outpatient setting. Atypical lower-extremity ulcers that are secondary to rheumatologic disorders and/or hematologic disorders are often very painful. The pain-remediating components of this xenograft extracellular matrix make it very appealing for such patients. Finally, with regard to burns and trauma, this can be a nice adjunct to heavily contaminated wounds that can go on to be skin-grafted very early.

POLYURETHANE FOAM WITH A POLYURETHANE COVER (NOVOSORB® BTM (BIODEGRADABLE TEMPORIZING MATRIX), POLYNOVO)

Mechanism of action

This product has no activity against infection or bacterial invasion; it simply cannot become infected. It is a "synthetic dermal replacement scaffold that is composed of polyurethane open-cell foam".[21] This material was originally developed as a burn dressing. The concept was that it could act as a temporizing dressing prior to split-thickness skin grafting after tangential debridement. The polyurethane open cell foam (BTM) allowed for the integration of vascular tissue and the ingrowth of surrounding collagen fibers to create a "neodermis." This "neodermis" is associated with high graft take rates for split-thickness skin grafts. The goal of having a new functional dermis is to provide a functional unit that allows for flexibility and good movement as well as reducing contraction and scarring, which predominantly occurs during the remodeling phase. The manufacturer's original secondary goals were "to provide a platform onto which an autologous cultured composite skin could be applied, therefore eliminating the need for extensive split-skin graft harvest." The actual 2 mm-thick foam is broken down by hydrolysis. However, the polyurethane seal on the surface is not broken down and is usually removed after 21 days.[21,22] An interesting concept surrounding this technology, in contrast to other dermal replacement technologies, is that since it is not biologic and does not have any collagen, it cannot become infected, or least it may provide significant resistance to infection.

Clinical data

In a prospective study in Australia, 10 patients were recruited, each of whom required surgery necessitating the harvest of an anterolateral thigh (ALT) flap (n=3), a fibular osseocutaneous (FOC) flap (n=3), or a radial/ulnar forearm (RF/UF) flap (n=4). The sterile BTM was cut to the shape of the wound and applied, seal uppermost, to the donor site. Its margin was secured with surgical staples. In ALT and FOC sites, a wound drain was inserted into deep potential spaces. The BTM was overdressed with Mepitel (Mölnlycke, Gothenburg, Sweden) and Acticoat (Smith & Nephew, Hull, UK) held with Hypafix (BSN Medical, Hamburg, Germany). Compression was afforded by a crêpe bandage. Subsequent similar dressing changes and wound assessments were performed every 3 to 4 days (twice weekly) by the investigators. At day 21, material delamination and grafting were scheduled to be performed. The appearance of fine granulations at the superficial surface combined with obscuring of the foam structure indicated integration with neovascularization. As the trial progressed, for reasons discussed later, the day of grafting varied. Localized infection was confirmed in 4 cases (40%). One of the infections appeared to be attributable to muscle necrosis, and the other 3 involved the BTM itself. In the necrotic muscle case, the BTM did not adhere over necrotic tissue and 16% was excised to debride muscle and drain the abscess. Two patients suffered a significant infection, which was treated non-operatively. In the other 2 patients, partial removal of the seal alone allowed fluid to escape and integration to continue without the removal of any BTM. In all of these cases, the remaining BTM persisted to integration and ultimately sustained split-skin graft take. Overall, the mean initial wound area decreased by 3.87% by the time of grafting (20-50 days).[22]

Li et al. treated 27 patients with 35 complex wounds.[23] There was a much lower infection rate in this group of patients than in a previous group. Once again, all of these patients had initial surgical debridement to remove all devitalized and infected tissue prior to placing the BTM. Interestingly, a topical silver dressing was placed over this product. In areas where there was a joint involved, a splint was used to reduce mobility. Negative pressure wound therapy was used in selected cases. The authors reported that 33 of 35 cases showed complete integration of the BTM prior to split-thickness skin grafting or other closure. Neither of the non-integration cases was noted to be secondary to infection.

Our own experience

Our center has used this product to treat 5 patients with highly colonized lower-extremity wounds. All of these applications were done in the operating room. Therefore, there has been a wide surgical excision of the base of the wound prior to application of the material (Fig. 3). In 4 of the 5 patients, we have had very good engraftment with removal of the outer membrane and explantation of

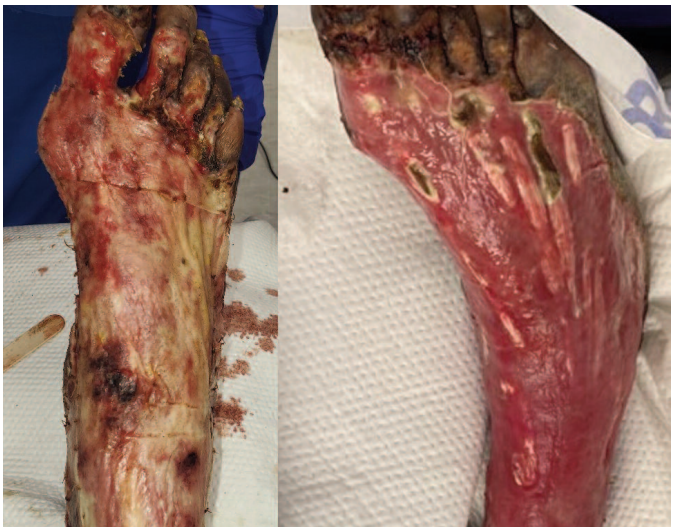

Figure 3. BTM applied under negative pressure wound therapy (left) and upon removal at Day 21 (right).

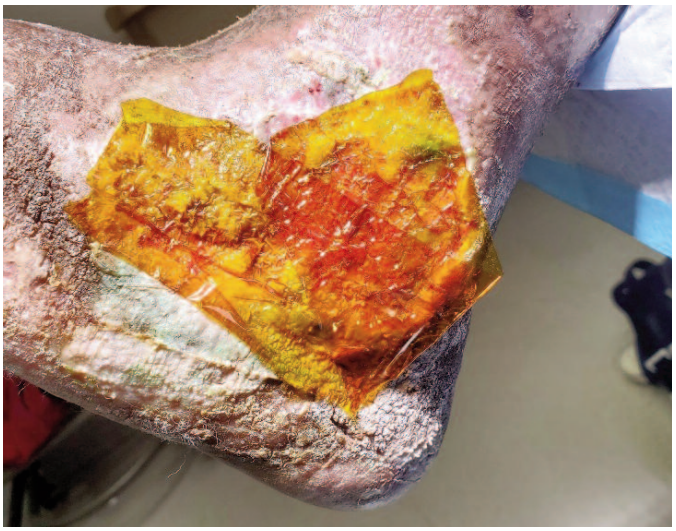

Figure 4. Application of a polyelectrolyte multilayer nanofilm and silver to a heavily colonized ankle wound.

the material at approximately day 21. The patients have undergone split-thickness skin grafting with successful outcomes and close to 100% take. The sole patient in whom the product was unsuccessful had a very dense infection, and the product sloughed off at day 7. Therefore, in our experience, it was relatively resistant to bacterial infection, but not completely resistant, which is similar to the results reported in the literature.

Best dosing or application strategy

Currently, this appears to be a single-application graft. In our cases, and in previous studies, the product is primarily used as a single-application material after surgical reconstruction. This is followed by skin grafting. We applied this graft in the operating room, and in most cases surgical staples were used to hold it in place. It can be used in conjunction with negative pressure wound therapy. Interestingly, in the prospective trials performed in Australia, topical silver dressings have been used on top of this polyurethane, but we suspect that this practice may not offer any value.

The manufacturer is pursuing a study to evaluate its use in the setting of outpatient diabetic foot ulcer and potentially in venous stasis disease. Regardless of the outcomes of these studies, based on the structure and maturity of this product, in most cases it is likely going to be a bridge product prior to application of a skin graft or other closure strategy. Notably, smaller wounds have been observed to epithelialize natively during follow-up.

Possible algorithms of care

Currently, use of this product makes the most sense in cases of very large partial and full-thickness injury. This product is much less expensive than other bridge therapies. Therefore, in burn therapy and significant soft tissue and degloving injuries, it is very attractive. This product can be made almost any size and therefore lends itself to large surface areas. Currently, we see this as a viable option for large body surface area injuries after the patient has undergone significant debridement. In one published series of 25 soft tissue defects, 3 were attributed to burns, 5 to scar revision, 7 to necrotizing soft tissue with infection, 3 to closure after tumor excision, and 7 to traumatic tissue loss. Most of these injuries (36%) were in the foot and ankle or hand and forearm (28%).[24] The authors noted that the primary contraindication for using this product was in areas that were poorly vascularized, specifically the foot and ankle.

DISSOLVABLE MATRIX WITH SILVER (MICROLYTE® MATRIX, IMBED BIOSCIENCES) PEMAG

Mechanism of action

This matrix is a synthetic resorbable polyelectrolyte multilayer (PEM) nanofilm composed of cationic polyallylamine hydrochloride and anionic polyacrylic acid, which is designed to act as a functional molecular template to facilitate granulation in the wound bed. The nanofilm matrix is coated with a 20-micron layer of polyvinyl alcohol (PVA) to provide moisture management and product handleability. The nanofilm matrix contains a low level of ionic and metallic silver ($<25\mu g/cm^2$) to prevent microbial contamination and colonization of the matrix. The PEMs act as a scaffold to support mammalian cell growth; it has been demonstrated that keratin sites spread more easily on silver-loaded PEMS than on a glass plate.[25] In the standard mouse full-thickness re-epithelialization model, wounds treated with PEMAG close faster and more completely then those treated solely with PEM and untreated wounds. The authors postulated that PEMs contain both anionic and cationic charged polymeric components which enhance the ability of granulation tissue to withstand the surface chemistry of the chronic wound. In addition, it is postulated that the structure of the PEM may allow for better silver delivery, as well as activity. Finally, hydrophilic PVA maintains a physiologic moist micro environment in the wound.[26]

Clinical data

A prospective study was carried out in 32 human subjects who had been previously treated unsuccessfully with traditional wound care regimens. These wounds included venous stasis ulcers, diabetic foot ulcers and postoperative surgical wounds as well as chronic non-pressure-related lower-extremity ulcers (what we would call atypical wounds). The in vitro killing rate was greater than a 4-log reduction in CFUs for clinically relevant microbes including MRSA and vancomycin-resistant Enterococci (VRE). The mean duration of these wounds was

40 weeks. The average wound closure rate was 66% at 3 weeks and 73% at 12 weeks.[27] This product is currently being studied in an open-label prospective trial run by Mission Health; the findings are scheduled to be reported by December 1, 2021. The study design included a targeted enrollment of 20 cases of venous stasis, 20 diabetic foot ulcers, 20 pressure ulcers and 40 patients with other types of wounds.

Our own experience

We have been using this product for both inpatients and outpatients (Fig. 4), and our outpatient experience is much more promising. In patients with atypical lower-extremity ulcerations, we have found this to be a very effective dressing when applied 3 times a week. In patients with rheumatoid or hematologic lower-extremity ulcerations, this film can be applied 3 times a week and adheres directly to the wound with almost no pain. The patients have shown a very high level of satisfaction with regard to self-care, hygiene, pain reduction, and clinical outcome. Of the 18 patients who we have treated with this therapy, 9 have experienced complete resolution of their wound.

There are many case reports of post-operative wounds, stalled venous stasis ulcers and a variety of other wounds. While members of our department have reported using this product in conjunction with advanced tissue therapy, we do not think this is a good idea since the product actually tends to dry out the wound bed very effectively. Overall, we have had better luck using this product to finish closing ulcers after using advanced tissue products.

In the inpatient setting, we use this product very differently. We have placed this in forefoot ulcerations after flap reconstruction. We have also placed it under transmetatarsal amputations, and are starting to place it in high-risk groin incisions. We are currently pursuing 3 QA projects regarding this product; one in high-risk incisions, one in sternotomies, and one in percutaneous access puncture sites.

Best dosing or application strategy

To date, we have had the best results in outpatients with a dosing strategy of 2 or 3 times a week. We usually have the patient place the product directly on their wound 3 times a week over a 2-week period, with 1 visit at our center out of the 6 applications. This is usually done in conjunction with a foam dressing with a silicone border, which is placed directly over the material. Patients experience a reduction in pain and, as noted previously, we have experienced a 50% closure rate in atypical ulcers. The duration to closure has been approximately 12 weeks. We also use this product over slowly healing or partially dehisced superficial wounds postoperatively, and have had very positive results. Currently, we have very little data to support using this product in high-risk wounds. While we and others certainly have anecdotal data to this effect, at the moment we have nothing that could be considered a strong clinical indication.

Possible algorithms of care

As noted above, atypical wounds and lower-extremity wounds with a high bioburden seem to do quite well with this dressing if it is changed frequently. In addition, postoperative minor wound dehiscence dries up very quickly with this product. We have also found that it is useful for finishing closure after using other cell- and tissue-based therapies. A definite area for exploration involves placing this product in high-risk surgical incisions.

CONCLUSION

There may be some collagen-based products other than those described here that have antimicrobial properties, as well as some pure antimicrobial therapies. We sought to discuss technologies that offer differing dosing regimens as well as differing mechanisms of action. We also sought to highlight that, for most of these products, there are very little data to support their clinical efficacy.

NCPHMB may have the strongest argument for a mechanism of action since PHMB has been very well studied as an antimicrobial agent. Omega 3-rich AFS also has a very compelling case for a mechanism of action, although Omega 3 fatty acids have not been particularly well-studied with regard to any antimicrobial properties. The quality of the data regarding the possible mechanism of action for silver added to FBD is comparable to that regarding the use of silver in general. Unfortunately, it is not available in the public domain for review, which makes the quality far weaker. BTM offers a somewhat novel explanation for its mechanism of action in that it simply is not a biologic agent and therefore is very difficult to actually become infected. In addition, clinical data are available to help support some of these claims.

In general, the five different technologies discussed also have very different dosing structures. NCPHMB and AFS can both be applied frequently in the outpatient setting. At our facility, NCPHMB costs 3 times as much as AFS. In the outpatient setting, for the treatment of an average venous stasis ulcer with 5 to 8 applications of either product; this represents a difference in cost of $9,000 to $14,000 USD. In the inpatient setting, with relatively similar outcomes and a faster time to grafting, it would appear that AFS has a significant cost-to-outcome advantage. However, NCPHMB may currently be more strongly supported by basic science to back up its antimicrobial claims. While very favorable data are available to support the use of PCPHMB for pressure ulcers, few studies have looked at extracellular matrix therapy for pressure ulcers.

As described above, BTM is really a bridge technology that is to be used prior to skin grafting. As such, it competes with silicone layer-covered bridges and dermal regenerative technologies. In this competition, it benefits from its inability to become infected. As a single-use product, BTM is currently only available in sizes that make sense in the inpatient setting; it is approximately 20% the cost of FBDAG. The question of whether BTM creates a neo-dermis that is structurally as flexible and functional as FBDAG has not yet been answered. While AFS has been used as a single-use application for burns and other large trauma injuries in the OR, BTM is approximately 40% of the cost of AFS. However, it is unlikely that skin graft could be applied within 1 week of the application of BTM, as is possible with AFS. We would like to see more data regarding how BTM fares in critically colonized animal models.

PEMAG is really in a class by itself since it is so less expensive than the other products. Indeed, its cost is so low that it may be worth asking "since it does no harm, why not?" In our experience, it has been a very favorable bridge out of using tissue-based therapy for some of our complex hard-to-heal lower-extremity wounds. It has provided very good results in the outpatient setting, especially in patients who would like to participate in full-body hygiene, as well as patients who prefer to have fewer office visits and

more oversight of their own care. We need to figure out how to use it in the inpatient setting to help reduce surgical site complications and infections.

In closing, as tissue- and matrix-based therapies continue to become more a part of our daily wound-closure and wound-treatment strategy, it is desirable to have matrix technologies that do more than one thing. An extracellular matrix that can both treat the wound and actively participate in wound bed preparation can help simplify our clinical pathways. Obviously, aggressive wound bed preparation is a key to success. However, access to a matrix-based dressing that can stand up to an inadequately prepared wound bed allows the clinician and, more importantly, the patient some additional leeway. STI

AUTHORS' DISCLOSURES

JL is a local principal investigator for Organogenesis (Canton, MA), Director of the Scientific Advisory Board and national principal investigator for Kerecis (Isafjordur, Iceland), and a consultant and national principal investigator for Integra Life Sciences (Princeton, NJ). The other authors declare that there are no conflicts of interest.

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