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Treatment of ulcerated necrobiosis lipoidica with ovine forestomach matrix

Necrobiosis lipodica (NL) results from degradation of the collagen extracellular matrix; these recurring ulcerated lesions are an especially challenging condition to treat. Ovine forestomach matrix (OFM) is a decellularised extracellular matrix and was used to successfully close a pretibial ulcer resulting from NL. Complete closure of the wound was achieved in 22 weeks, after four applications of OFM. This suggests OFM may be considered for the treatment of these challenging wounds.

ovine forestomach matrix; necrobiosis lipoidica; wound healing; chronic ulcer; extracellular matrix

Decellularised extracellular matrix (dECM) biomaterials are at the forefront of new technologies developed to arrest the growing burden of chronic wounds.[1] They are primarily composed of collagens I and III, in the form of native fibres that mimic normal-tissue ECM. There are also secondary molecules present, such as structural, adhesion and signalling molecules, which associate with the collagen matrix and mediate cellular processes during tissue regeneration.[2]

Ovine forestomach matrix (OFM) is a dECM-based product that has received regulatory clearance for wound repair and regeneration in the United States. OFM comprises a heterogeneous mixture of ECM molecules, including collagens I, III and IV, elastin, fibronectin, laminin, glycosaminoglycans and hyaluronic acid.[3] In pre-clinical studies, it has been shown to stimulate endothelial cell migration and proliferation, and is angioinductive in preclinical models.[4] A clinical evaluation of OFM in venous leg ulcers observed positive changes in the wound bed of the treated wounds.[5]

This report presents a clinical evaluation of OFM for the treatment of necrobiosis lipoidica (NL), a granulomatous skin disease of unknown aetiology that is often associated with diabetes mellitus.[6,7] In some instances, NL presents as recurring ulcerated lesions.[7] Although the exact cause of NL is not known, it is an inflammatory disorder characterised by collagen degeneration, with a concomitant granulomatous response. Lesions typically result following mechanical damage to the underlying collagen fibres of the dermis, often leading to persistent ulcerations that are challenging to heal.[7]

Given that NL is linked with degeneration of the ECM, we sought to investigate whether the underlying necrosis could be corrected by the application of OFM. To our knowledge, this case study reports the first instance of the successful treatment of NL using a dECM-based product.

Case study

A 61-year-old woman, without diabetes mellitus, presenting with two chronic pretibial ulcerations, of total wound area 11.5cm^2 (depth 3.3mm), was enrolled as part of a larger, institutional review board-approved study (Upper South B Regional Ethics Committee, New Zealand). The ulcers had been present for 28 years and diagnosed as NL on biopsy, 8 and 5 years previously. Numerous surgical and medical treatments had been attempted during this time, including excision, systemic steroids and intralesional steroids.

The wounds were debrided of slough by a light scraping of the wound bed with a no. 10 scalpel, followed by gentle saline irrigation. The wounds were digitally imaged (EOS, Canon Incorporated) and surface area and depth measured using digital planimetry (Silhouette, ARANZ Medical).

The size of the OFM matrix (Endoform, Mesynthes Ltd.) was selected to provide complete coverage of the wound bed, and was trimmed prior to application, so it inset and met the wound margins. The matrix was applied to the wound bed and then rehydrated with sterile saline, as needed. OFM was covered with a non-adherent dressing, either Mepitel (Mölnlycke Health Care) or Cuticerin (Smith & Nephew), and gauze (Propax; BSN Medical), and then secured in place with a protective stockinet

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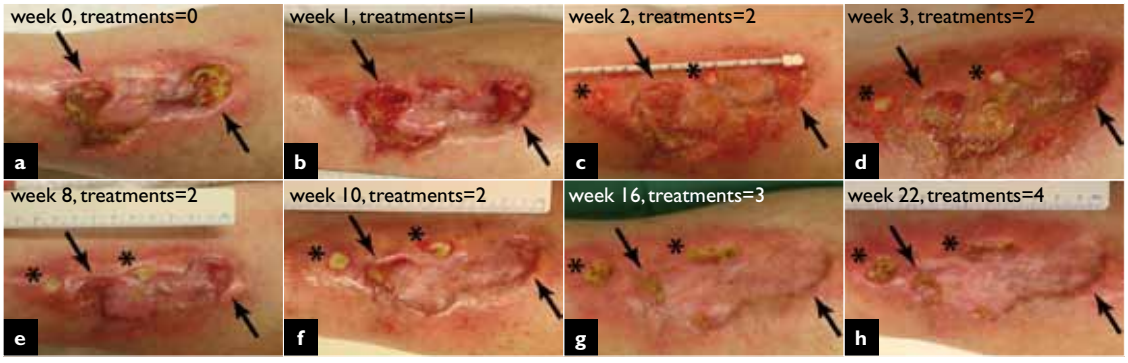

Fig 1. Treatment of ulcerated necrobiosis lipoidica with OFM, showing ulcers on presentation (a), and throughout treatment (b–g); full healing was achieved by week 22, after four applications (h). Black arrows indicate the wounds enrolled in the study; *subsequent wounds that developed during the course of the study

(Tubigrip; Mölnlycke Health Care). These dressings ensured that the matrix conformed to, and was in contact with, the underlying wound bed.

Secondary dressings and antimicrobial dressings (such as Aquacel Ag; ConvaTec) were used according to standard practice. Medications were not altered during the study and no adjuvant treatments were applied within 6 months of the study period.

The matrix was re-applied on weeks 2, 11 and 16, with a total of four applications over a 24-week period. At the time of re-application, the wounds were debrided as necessary (described above), imaged and the wound dimensions measured. The dressing was reapplied and dressed, as described above.

Following application, OFM was found to conform well to the underlying wound bed and became adherent in 2–3 days. Over the course of 1–4 weeks, noticeable changes in the morphology of the matrix were observed, with the formation of an off-white to golden gel, resulting from remodelling and incorporation of the matrix into the wound bed.[5]

Total wound area at the initial visit was 11.5cm^2 (depth 3.3mm). By weeks 8 and 10, the total wound area had decreased to 37% (4.2cm^2) and 18% (2.0cm^2) of the original wound area, respectively. Positive changes in the appearance of the wound bed, including reddening and formation of granulation tissue, were noted following the first application (Fig 1a–e).

Opportunistic infection of the wounds was noted at week 2, which was resolved by use of a silver-containing dressing (Aquacel Ag; Fig 1c,d). The application of the silver dressing did not grossly impact on the underlying OFM. Robust epithelialisation of the wound was noted at 6–8 weeks and complete closure had occurred at 22 weeks (Fig 1h). During the course of treatment, two additional ulcerations developed adjacent to the treated wounds (Fig 1c). These additional wounds were treated with standard care only.

Discussion

To our knowledge, this is the first example in the literature of ulcerative NL being successfully treated using a dECM-based product. Outside of standard care, there are few established treatment options for NL and it is considered challenging to treat.[8] Experimental interventions have included small molecule bioactives, such as corticosteroids, anti-TNF agents and thalidomide,[9] ultraviolet A (UVA) phototherapy,[10] negative pressure wound therapy,[11] and collagen-based dressings.[12]

Given the mechanism of action of dECM-based matrices, it is interesting to speculate on the positive role these products could play in correcting the imbalance seen in ulcerated NL. Studies have demonstrated that collagen and elastin degradation and structural abnormalities underlie NL, with an associated reduction in fibroblast production of ECM components.[13] Therefore, a rational approach to therapeutic intervention would be to replace the compromised ECM with exogenous ECM components, such as those found in OFM. Additionally, dECM materials may correct the granulomatous inflammation seen in this disease. The inflammatory response to dECM-based matrices is consistent with normal tissue turn-over, and the macrophage phenotype in response to dECMs is considered to be immunomodulatory.[14] Therefore dECMs may tip the balance of the wound environment towards constructive remodelling.

OFM is indicated for re-application every 5–7 days, while the current study used a re-application of 2–8 weeks. This conservative approach was deliberately adopted as the response of NL to the dECM-based matrices was unknown. From clinical observation, there was no difference between the behaviour of OFM in the NL wounds and other chronic wounds. This suggests that future treatments of ulcerative NL lesions could employ a higher re-application frequency of OFM as indicated (every 5–7 days). Higher re-application rates (every 5–7 days) would increase the availability of ECM components in the wound bed.

Conclusion

It is possible that OFM may represent a useful adjunct therapy for the management of NL. Given the absence of an effective standard of care for ulcerative NL, the findings here suggest that further studies are warranted to fully assess the suitability of OFM for the treatment of these challenging wounds. ■

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Ovine Forestomach Matrix as a Substrate for Single-Stage Split-Thickness Graft Reconstruction

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Keywords: biomaterial, carcinoma, ovine forestomach matrix, reconstruction, split-thickness graft

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Objective: Split skin graft reconstruction of scalp defects often leaves an obvious contour defect. Here, we aimed to demonstrate the use of a decellularized extracellular matrix biomaterial, termed ovine forestomach matrix (OFM), as a substrate for split-thickness skin grafts (STSGs) for scalp reconstruction. **Methods:** Following full-thickness tumor excision, OFM was applied directly to skull periosteum, and then an STSG was applied. Participants were monitored for graft take, epithelialization, and cosmetic outcomes. **Results:** Participants responded well to the procedure with more than 95% graft take in 4 participants, and 100% epithelialization of the grafts after 2 weeks. A 30% graft take was observed in the fifth participant due to local infection and partial necrosis of the graft. Ovine forestomach matrix was remodelled with time and the regenerated dermis was well vascularized and had robust and ordered collagen deposition. **Conclusions:** This series demonstrates that OFM can serve as a temporary dermal scaffold to support an overlying STSG and allow for a single-stage grafting procedure.

Reconstruction of skin defects may be performed by skin grafting procedures. Full-thickness skin grafts result in a more durable reconstruction due to the larger proportion of dermis placed into the defect than split-thickness skin grafts (STSGs). Because of limited full-thickness skin graft donor sites, STSGs are used in larger defects. Two-stage grafting procedures have been developed whereby a dermal substitute is grafted into the defect under an artificial epidermis, which is subsequently replaced by an STSG. There is a clinical need to replace the relative complexity of 2-stage grafting procedures with robust single-stage procedures without compromising clinical outcomes. However, the feasibility and success of single-stage procedures is dependent on the vascularity of the underlying tissue. To overcome these limitations, collagen-based dermal substitutes have been investigated as temporary substrates for an overlying STSG. This approach creates a composite graft, whereby the underlying dermal substitute is rapidly vascularized and therefore can

support epithelial proliferation of the STSG, leading to closure of the defect and dermal regeneration. The dermal substitute, human acellular dermal matrix (eg, Alloderm) has been investigated for STSG composite grafting in the treatment of burns,[1-3] traumatic skin loss,[2,4,5] and tumor excision.[6-8]

Ovine forestomach matrix (OFM) is a decellularized extracellular matrix biomaterial developed for wound healing and tissue regeneration applications and is cleared by the US Food and Drug Administration for dermal indications. Ovine forestomach matrix comprises mainly collagens I and III arranged as native fibres that retain the 3-dimensional architecture seen in tissue ECM.[9] Additional structural (eg, collagen IV, fibronectin, and elastin), signalling (eg, glycosaminoglycans and heparin sulphate), and adhesion molecules (eg, laminin) are also present. Ovine forestomach matrix is nonantigenic, and it undergoes cellular infiltration and subsequent remodelling leading to regeneration of missing or damaged tissues. In preclinical models, OFM has been shown to be angioinductive and is rapidly revascularized,[10] and in clinical studies, OFM treatment resulted in well vascularized granulation tissue in chronic venous ulcers.[11] These previous findings suggested that OFM may be suitable for composite grafting with STSGs, where clinical success is reliant on the ability for the substrate to rapidly revascularized and provide the requisite nutrients and immune components to the overlying STSG.

METHODS

Case studies

The case series was approved by an institutional review board (Upper South A Regional Ethics Committee, New Zealand) and registered with the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au/). Five participants were selected on the basis of the inclusion and exclusion criteria listed in Table 1 and all tumors were confirmed by pathology prior to the procedure. The procedure was conducted under either local or general anesthetic. A full-thickness excision down to but not including the pericranium was used to remove the tumor and a 5- to 10-mm margin (Fig 1a). Ovine forestomach matrix (Endoform, Mesynthes Limited, New Zealand) was meshed by either hand or a skin graft mesher at a ratio of 1.5:1 (Zimmer) and then trimmed to fit the excisional defect. The material was rehydrated in sterile saline for a minimum of 5 minutes and placed into the defect to contact the underlying periosteum (Fig 1b). An STSG (approximately 0.25-mm thick) was harvested from the thigh of each participant, using either a dermatome (Zimmer Machinery Corporation, Cowpens, South Carolina) or a hand knife. The graft was meshed by hand, cut to fit the defect, and then placed over the OFM, making sure the OFM and STSG were in contact (Fig 1c). A nonadherent dressing (Mepitel, Mölnlycke Health Care, Sweden) was placed over the graft, then a bolster of foam was sutured in place to ensure close contact between the STSG, OFM, and underlying periosteum (Fig 1d). The secondary dressing was removed 7 days following surgery and the graft imaged and evaluated for percentage graft take and epithelialization, based on the total area of the defect. A silver-based hydrogel (Silvasorb; Medline Industries, Inc, Mundelein, Illinois) was used to treat any suspected bacterial infection. The defect was re-dressed using a nonadherent dressing, as required,

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and reevaluated weekly for the first fortnight, then monthly or as required. At final review, the healed wounds were assessed for contour defect and scalp mobility by palpation.

Table 1. *Inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria
>18 years old	Any cutaneous malignancies with metastatic disease
At least 1 nonmelanoma skin cancer without metastatic disease	Diagnosed with malignant melanoma
Malignancies that require full-thickness excision	Systemic malignancy
Postexcision wounds that would normally be reconstructed with a split skin graft	Under suspicion of metastatic disease
Compliant	Pregnant or lactating
Competent	Clinically significant cardiac, pulmonary, renal, hepatic, neurologic, and/or immune dysfunction that may affect wound healing
Tumor located on the scalp, neck, or upper limbs	Known allergy to collagen or ovine (sheep) materials; any previous reaction to a collagen product
	Family or personal history of severe allergies (including asthma, hay fever, and atopic dermatitis)
	Allergies to foods, especially meat products
	Unable to remain in study for 6 mo
	Diabetes mellitus
	Declined, unable, or unwilling to make informed consent
	Not fluent in English or Maori—requires interpreter
	Religious or ethical objections to sheep-derived product
	Previous radiotherapy at the defect site
	Immunosuppressant medication (prednisone >5 mg/d or equivalent)

Histology and immunohistochemistry

Excised tissues were fixed with 4% formalin, paraffin embedded and stained. Gomoris' Trichome staining was conducted as previously described.[10] Anti-CD34 immunohistochemistry was conducted as previously described[10] using a mouse antihuman CD34 (Abcam Plc, Cambridge, England) monoclonal antibody. Slides were imaged using a CX-31 microscope (Olympus Imaging America Inc, Center Valley, Pennsylvania) fitted with a DP12 digital camera (Olympus).

RESULTS

Participants (B001 through B005) enrolled in the study were all male, 61 to 83 years old, presenting with either an squamous cell carcinoma (SCC) (n = 4) or basal-cell carcinoma (BCC) (n = 1), located on the scalp (Table 2). The tumor size, estimated at enrolment, ranged from 1.2 to 4.6 cm^2, and tumors had been present for approximately 2.5 to 9

months. Following tumor excision, the full-thickness wounds were approximately 5 to 10 cm^2. Ovine forestomach matrix could be meshed using a surgical skin graft mesher and once rehydrated was easy to handle and conformed well to the underlying periosteum. One week postsurgery, 4 of the participants had more than 95% graft take (B002, B003, B004, and B005), while the fifth participant, B001, had a 30% graft take. The low graft take in participant B001 resulted from a local infection and partial necrosis of the graft (Fig 2b), which was managed with a silver-containing hydrogel. Complete epithelization of all grafts occurred in 2 weeks, except for participant B001 where infection delayed complete epithelialization to 8 weeks.

Table 2. *Summary of participant details and outcomes*

Participant	Sex	Age	Tumor location	Age, mo	Type	Area, cm^2
B001	Male	83	Left vertex scalp	4	SCC	1.5
B002	Male	83	Left anterior scalp	9	BCC	1.2
B003	Male	73	Vertex scalp	8	Previous SCC	16.0
B004	Male	81	Left vertex scalp	2.5	SCC	2.9
B005	Male	61	Left vertex scalp	6	SCC	4.6

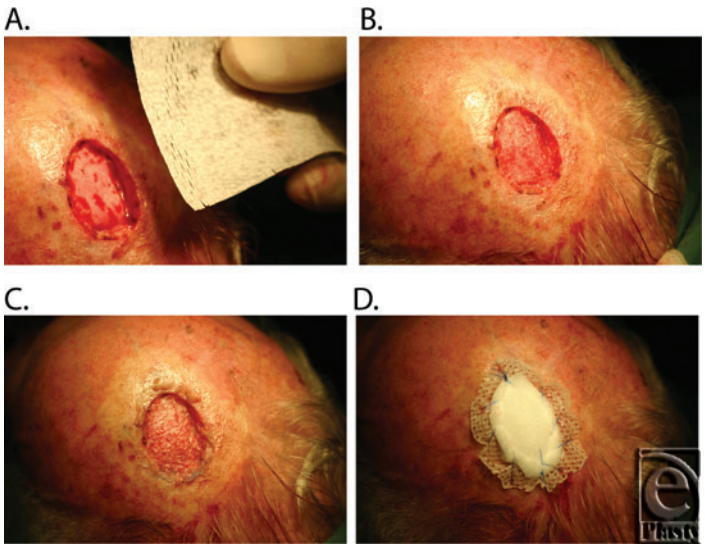

Figure 1. Representative images of the tumor resection and single-stage split-thickness grafting. (*a*) Excisional defect following tumor excision and meshed OFM prior to rehydration. (*b*) Rehydrated OFM cut to size and placed within the defect to conform to the underlying periosteum. (*c*) Meshed STSG in contact with the underlying OFM. (*d*) Secondary dressings secured to the perimeter of the excision.

Participants B001, B002, and B003 were available for long-term follow-up (Fig 2). The epithelium remained stable throughout follow-up (minimum follow-up of 6 months, range 7-9 months). Regenerated dermal tissues were well vascularized, elastic, and mobile over the underlying periosteum. Contour defects were judged to be mild via subjective observation.

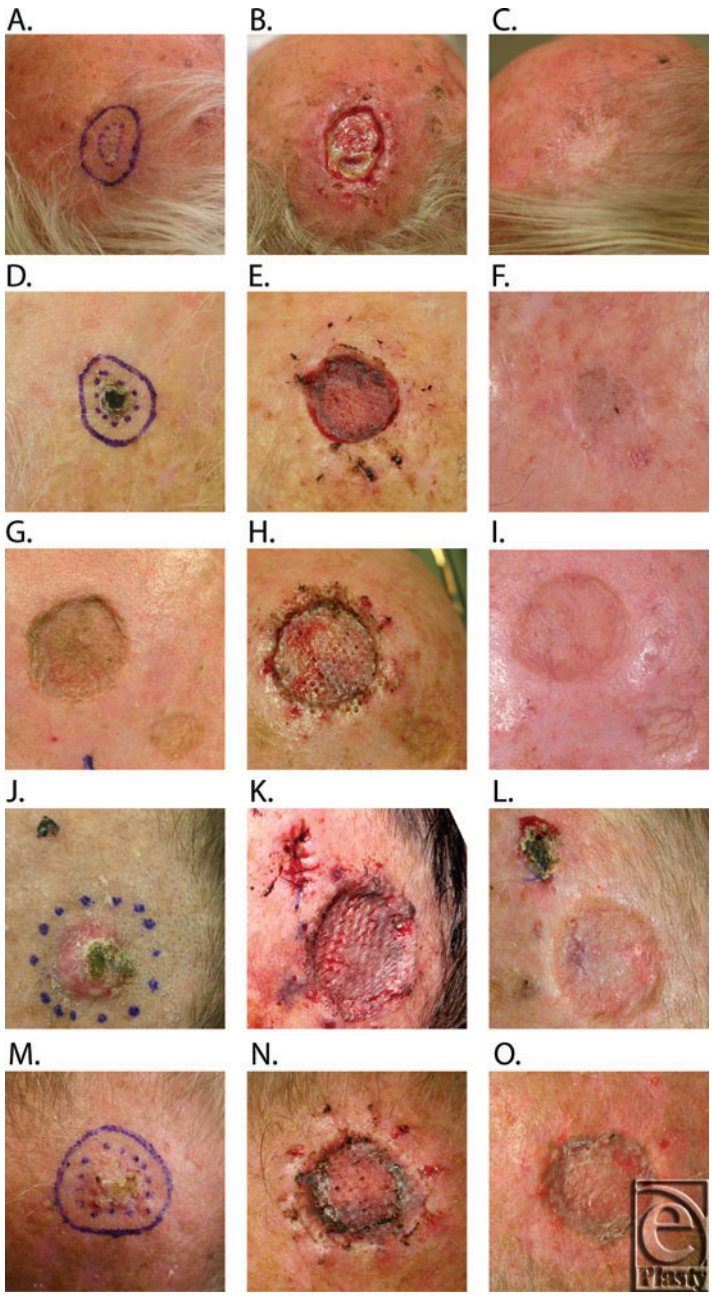

Figure 2. Representative images of the study participants B001 (2.A., 2.B., 2.C.), B002 (2.D., 2.E., 2.F.), B003 (2.G., 2.H., 2.I.), B004 (2.J., 2.K., 2.L.), and B005 (2.M., 2.N., 2.O.), prior to tumor excision (2.A., 2.D., 2.G., 2.J., 2.M.) and 1 week following surgery (2.B., 2.E., 2.H., 2.K., 2.N.). Surgical site following healing; 2.C., 40 weeks; 2.E., 16 weeks; 2.I., 16 weeks; 2.L., 4 weeks (prior to reexcision); 2.O., 4 weeks (prior to reexcision).

Two of the participants (B004 and B005) had the original surgical site further excised 4 weeks postsurgery to gain adequate (>1 mm histological margin) excision of the tumors at the deep margin. The subsequent procedure excised the original graft as well as the margins and underlying periosteum leaving exposed skull. Therefore, the defects were closed with scalp rotation flaps. The excised tissues containing the original graft were fixed, stained, and imaged (Fig 3a). Remnants of the matrix was evident in both B004 and B005 appearing as compact blue collagen fibers that were distinct from collagen of the regenerating dermis. The matrix was evident in the upper sections of the regenerating dermis, immediately beneath the superficial dermis from the STSG. Matrix fragments were infiltrated with fibroblasts and immune cells, including multinuclear giant cells (MNGCs) macrophages and lymphocytes. The immune response in B005 was greater than that in B004, with mononuclear cells and MNGCs associated with the remodelled matrix. Both patients had a well-vascularized dermal layer with dense well-organized collagen bundles and spindle-shaped fibroblasts (Fig 3a). A fully formed keratinized stratified squamous epithelial layer was present and dermal papillae extended into the epithelial layer. An extensive network of blood vessels was present within the regenerating dermis, as evidenced by anti-CD34 immunohistochemistry (Fig 3b).

DISCUSSION

Scalp reconstruction is especially challenging given the limited blood supply of the underlying calvaria, the relatively thin cutaneous tissue, and the lack of redundant skin. Split-thickness skin grafts take well on the underlying periosteum; however, this leaves an obvious contour defect. Skin flaps and expanders have been traditionally used, but these approaches are complicated by the minimal laxity of the scalp and the complexity of these multistage procedures. As an alternative, collagen-based biomaterials that function as temporary dermal scaffolds have become increasingly useful as part of a single- or 2-stage procedure for surgical reconstruction. These materials allow direct grafting to the underlying calvaria, usually following removal of the outer portion of exposed bone to allow vascularization of the dermal scaffold.[7,12,13] There are a few examples in the literature where dermal scaffolds have been used directly in contact with exposed pericranium to support an STSG,[8] and to our knowledge this is the first report of a xenogenic dermal scaffold being used in this fashion. The current composite grafting procedure allows for a single-stage procedure to be completed, therefore reducing increased costs associated with multiple procedures and longer term wound management. Results from the 5 participants enrolled in the current study indicate that clinical outcomes from this approach were not compromised, though further controlled studies are warranted.

Previous preclinical studies have shown OFM is remodelled, and importantly the remodelling phenotype resolves with time, with concomitant deposition of new tissues.[10] This is consistent with the known inflammatory response invoked by decellularized extracellular matrix–based biomaterials, namely remodelling as characterized by an immunomodulatory M2 macrophage phenotype rather an acute inflammation.[14] The current study provided a rare opportunity to microscopically examine a snapshot of the remodelling of OFM following human implantation, be it with a limited sample size. As has been seen previously in in vivo studies,[10,15] the inflammatory response to OFM included the recruitment of a number

of immune modulatory cells, including lymphocytes, macrophages, and MNGCs. Long-term resolution of the remodelling inflammatory response in participants was evidenced by the robustness of the regenerated dermis and absence of any wound breakdown.

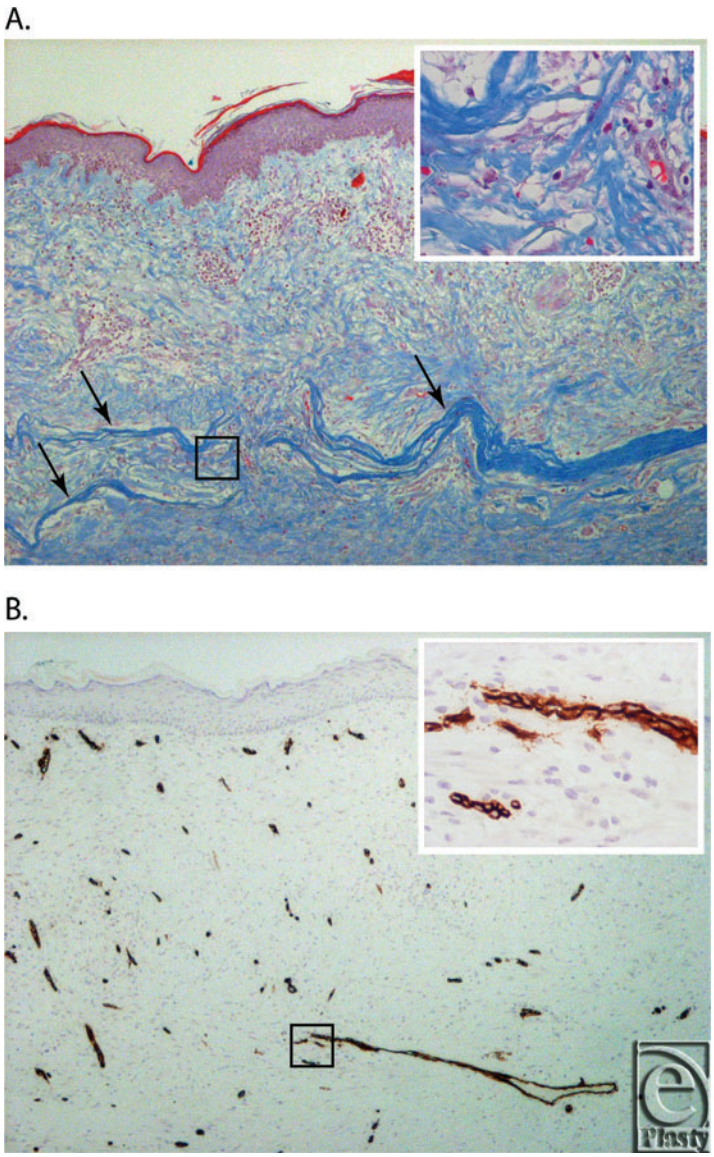

Figure 3. (*a*) Gomori's Trichome stain of the excised graft from B004, 4 weeks postgraft (4× magnification). Arrows indicate the intact fragments of OFM. Insert shows a 40× magnification of the area indicated by the black square. (*b*) CD34 immunohistochemistry of the excised graft from B004, 4 weeks postgraft (4× magnification). Insert shows a 40× magnification of the area indicated by the black square.

While the current application of this procedure was in the reconstruction of tissue deficits following tumor resection, there is the potential for this approach to be applied to the treatment of burns and traumatic skin loss. This initial study also suggests OFM as a candidate substrate for autologous cell seeding, whereby suspensions of dermal cells (eg, keratinocytes or fibroblasts) or stem cells (eg, bone marrow or adipose-derived stem cells) are applied to the substrate. This strategy has many similarities to the composite STSG procedure described here, as it relies on rapid vascularization of the underlying dermal scaffold to support the transplanted cells.

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Clinical Outcomes Following the Use of Ovine Forestomach Matrix (Endoform Dermal Template) to Treat Chronic Wounds

Brock A. Liden, DPM, and Barnaby C. H. May, PhD

ABSTRACT

The suitability of the ovine forestomach matrix (OFM) for the treatment of recalcitrant wounds was evaluated in 19 patients. At 12 weeks, 50% of wounds had closed, and the average reduction in surface area was 73.4%. Promising outcomes of this initial series support the clinical consideration of OFM.

KEYWORDS: ovine forestomach matrix, chronic wound, venous ulcer, diabetic ulcer

ADV SKIN WOUND CARE 2013;26:164–7

INTRODUCTION

Chronic wounds are characterized by a complex etiology that, in addition to an underlying medical condition, can also include aberrant cell–extracellular matrix (ECM) interactions, imbalances of matrix metalloproteinases, bioburden, and bacterial biofilm, and an unresolved inflammatory response—all of which contribute to the disruption or damage of the ECM.[1] Extracellular matrix components are important during tissue regeneration as they provide an essential pool of signals and substrates for cellular migration, proliferation, and differentiation.[2] Decellularized ECM (dECM)–based biomaterials have been developed to overcome tissue ECM deficits by providing a native collagen structure and functional secondary macromolecules to orchestrate tissue regeneration with concomitant capillary ingrowth.[3]

A dECM-based biomaterial termed "ovine forestomach matrix" (OFM) (Endoform Dermal Template; Mesynthes Ltd, Lower Hutt, New Zealand) has been cleared by the US Food and Drug Administration for dermal applications, including chronic wounds. Ovine forestomach matrix retains the authentic structure of native tissue ECM[4] and a complex mix of ECM-associated secondary molecules, whereas cellular and antigenic components (eg, cell debris and nucleic acids) are removed.[5] Although processed OFM is predominantly composed of collagens I and III, also present are elastin, fibronectin, laminin, and glycosaminoglycans.[5] Ovine forestomach matrix has been shown in vivo to support cell attachment and differentiation and is completely remodeled during the regenerative process.[6] Based on positive preclinical findings, a study was conducted to evaluate OFM in treating lower-extremity wounds.

METHODS

Participants with at least 1 chronic, lower-extremity wound were enrolled with consent in a prospective, noncomparative, open-label evaluation. Inclusion and exclusion criteria are described in Table 1. Product indications, contraindications, and precautions were followed (Table 2). All wounds were surgically debrided and irrigated with hypochlorous acid solution (Vashe Wound Therapy; PuriCore, Malvern, Pennsylvania) prior to a 7-day qualifying period. During the qualifying period, chronic wounds resulting from a prior surgery and venous ulcers were treated with a silver calcium alginate dressing and compression, whereas diabetic foot ulcers were treated with once-daily collagenase ointment and off-loading. Following the qualifying period, wounds remaining free of visible symptoms of infection were continued in the study, and silver calcium alginate dressings and collagenase ointment treatments were stopped.

Table 1.

STUDY INCLUSION AND EXCLUSION CRITERIA

Inclusion	Exclusion
Patient ≥18 y old	Exposed bone, tendon, or fascia
Noninfected chronic venous, arterial, incisional, and diabetic wounds	Wound over bony prominence
Wound duration ≥1 mo	Visible signs of infection (swelling, pain, purulent drainage, or tracking into the deep tissue planes) following a 7-d qualifying period
	Third-degree burns
	Known sensitivity to ovine or collagen materials
	Unable to remain in trial for 12 wk or until wound epithelialized (whichever shorter)
	Declined, unable, or unwilling to make informed consent

Dr Liden is Owner, Reynoldsburg Podiatry Centre, Reynoldsburg, Ohio. Dr May is Scientific Director, Mesynthes Limited, Lower Hutt, New Zealand. Dr Liden has disclosed that he has no financial relationships related to this article. Dr May has disclosed that he is a shareholder in Mesynthes Limited. Acknowledgment: The authors thank Karen Beach for assistance in preparing this manuscript. Submitted February 16, 2012; accepted in revised form September 13, 2012.

Table 2.

OFM INDICATIONS, CONTRAINDICATIONS, AND PRECAUTIONS FOR USE

Indications	Contraindications	Precautions
Partial- and full-thickness wounds	Known sensitivity to ovine (or collagen material)	Uncontrolled clinical infection
Pressure ulcers	Third-degree burns	Acute inflammation
Venous ulcers		Excessive exudate
Diabetic ulcers		Excessive bleeding
Chronic vascular ulcers		
Surgical wounds		
Traumatic wounds		
Draining wounds		
Tunneled/undermined wounds		

Using aseptic technique, OFM was trimmed to slightly overlap the wound margins, placed on the wound bed, and rehydrated with sterile saline until moist. Light pressure was applied to the matrix to ensure conformity to the underlying wound bed, and the OFM was secured with a nonadherent secondary dressing. Compression stockings, exudate control, and off-loading were used as required.

At follow-up appointments (weekly or less frequently), wounds were debrided and irrigated to remove loose debris, residual OFM that appeared in the wound bed as an off-white gel was left in place, and OFM was reapplied. Changes in granulation tissue and wound dimensions were recorded, and the wound was photographed. Application of OFM was discontinued when the wound was partially or fully re-epithelialized, or at the end of 12 weeks. Demographic and wound healing data were analyzed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

This series consisted of 19 participants with 24 wounds. Demographic and outcomes data are summarized in Tables 3 and 4. The mean wound area decrease at study end was 73.4%, and the average weekly wound area decrease was 0.259 cm^2, as determined through linear regression. There was no correlation between initial wound size and time to healing (Spearman correlation, $P = .09$). Of the 24 wounds, 8 (33%) were closed by 8 weeks of treatment, and this number increased to 12 (50%) at 12 weeks (Tables 4 and 5). The mean time to closure was 7.3 weeks for the 12 wounds (50%) that had completely closed at 12 weeks. Given that the remaining 12 wounds were still open after 12 weeks of treatment, the mean time to complete closure for all wounds could not be calculated. Mean duration of OFM treatment was 5.9 weeks, and mean time between clinic follow-up visits/OFM reapplication was 8.5 days. No serious adverse events were reported. The physician found the OFM easy to apply. Cases are highlighted in Figures 1 and 2.

Table 4.

FREQUENCY OF COMPLETE WOUND CLOSURE BY WOUND TYPE

Wound Type	Total Completely Closed (%)
Pressure ulcer	0/1 (0)
Chronic surgical wound	2/4 (50)
Venous stasis ulcer	2/5 (40)
DFU	8/14 (57)

Abbreviation: DFU, diabetic foot ulcer.

DISCUSSION

Wound dimensions decreased in 21 of 24 wounds, including patients with multiple comorbidities. Of the 2 wounds that increased n wound area, 1 (wound 23) was treated for only 7 days then lost to follow-up, and 1 wound (wound 6) became infected. The infection was thought to be unrelated to OFM and was treated with a silver-containing dressing (over the OFM) and systemic antibiotics. The silver dressing did not appear to negatively impact the underlying OFM. The infection resolved within 2 weeks, and OFM treatment was continued. Because of differences in study designs and samples, the authors' results are not directly comparable with existing wound studies. For example, some wounds (n = 7) enrolled in the study were less than 1 cm^2 in area and therefore may have closed with

Table 3.

SUMMARY OF PARTICIPANT DEMOGRAPHICS

Mean Age, y	Sex (n)	Wound Type/ Etiology (n)	Wound Location (n)	Mean Surface Area of Wounds at Initial Visit, cm^2	Mean No. of Visits	Mean Treatment Time, wk	Mean Time Between Follow-up Visits, d
61 (SD, 12.9; range, 19–84)	M (9)	DFU (14)	Leg (7)	3.0 (SD, 3.9; range, 0.1–14.8)	5 (range, 1–23)	5.9 (range, 1–12)	8.5 (range, 5–21)
	F (10)	Pressure ulcer (1) Chronic surgical wound (4) Venous stasis ulcer (5)	Toe/foot (17)				

Abbreviation: DFU, diabetic foot ulcer.

Table 5.

WOUND CLOSURE RESULTS WITH OFM

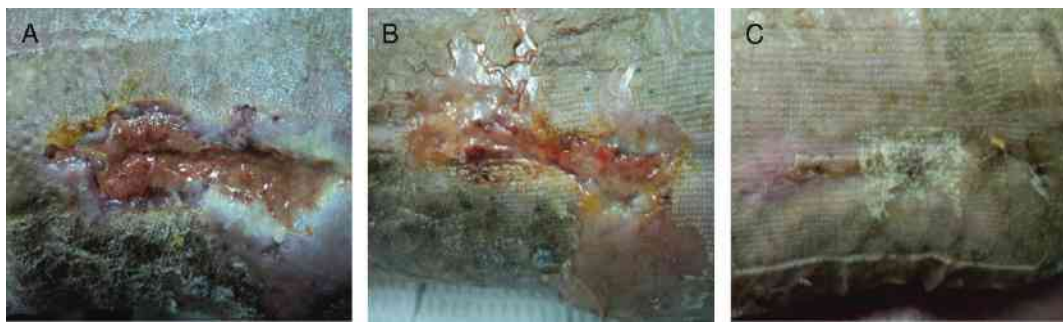
Wound No.	Age, y	Sex	Wound Type	Wound Duration, wk	Initial Wound Area (T = 0 wk), cm^2	Total OFM Treatments	Wound Area at End of Patient Study Period, cm^2	% Closure at End of Patient Study Period	Total Time to Closure, wk
1	60	F	VSU	12+	14.8	9	0.0	100	11.3
2	58	M	Surgical (foot)	4–6	5.0	6	0.0	100	7.0
3	41	M	DFU	4–6	2.6	6	0.0	100	6.9
4	56	F	DFU	12+	2.6	8	0.0	100	11.1
5	64	F	VSU	12+	1.4	6	0.0	100	8.9
6			VSU	12+	1.4	17	5.2	−271	
7			VSU	4–6	1.7	3	0.3	82	
8	69	M	DFU	4–6	1.2	9	0.0	100	9.9
9	67	M	DFU	12+	1.8	4	0.0	100	4.9
10	56	F	DFU	Unknown	1.3	6	0.3	77	
11	57	F	DFU	Unknown	2.9	3	0.9	69	
12			DFU	Unknown	10.9	3	7.4	32	
13	75	M	DFU	4–6	1.9	5	0.4	79	
14			DFU	4–6	3.5	6	0.3	91	
15	53	M	Surgical (ankle)	12+	8.7	8	0.0	100	8.0
16	70	M	DFU	4–6	0.9	6	0.0	100	6.9
17	84	F	DFU	4–6	0.9	2	0.0	100	1.9
18	64	F	DFU	6–12	0.2	3	0.0	100	3.0
19	50	F	Surgical (Achilles)	4–6	6.1	8	2.0	67	
20	60	F	DFU	4–6	0.1	2	0.0	100	2.0
21	72	F	PrU	Unknown	1.3	4	0.2	82	
22	56	M	DFU	Unknown	0.4	4	0.1	85	
23	72	F	VSU	Unknown	0.5	2	0.7	−44	
24	19	M	Surgical (foot)	4–6	0.2	1	0.2	0	

Abbreviations: DFU, diabetic foot ulcer; F, female; M, male; PrU, pressure ulcer; VSU, venous stasis ulcer.

standard care. Wounds in this series reached a 50% wound closure rate at 12 weeks, a finding consistent with the pivotal evaluation of small intestinal submucosa-treated diabetic wound closure rates (18/37; 49%) at 12 weeks.[7] Veves et al[8] reported a lower healing rate (37%) at 12 weeks of diabetic ulcers with collagen/oxidized regenerated cellulose matrix and an average wound area decrease

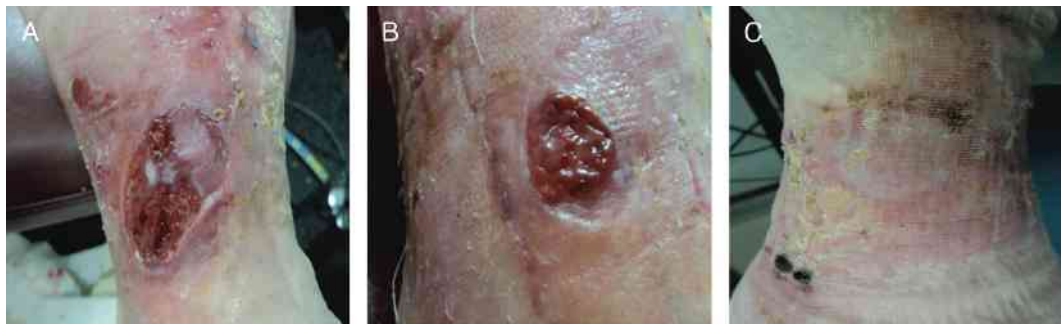
Figure 1.

CASE STUDY 1: VENOUS STASIS ULCER ON ANKLE



A, *T* = 0 weeks. Venous stasis ulcer of 2 years' duration on ankle. Patient had history of hypertension. Prior treatments included compression, debridement, collagenase enzymatic therapy, living cell–based product (x1), human fibroblast-derived dermal substitute (x8), porcine tissue bioscaffold, and xenograft. B, After 4 weeks of OFM treatment, wound was granulated, and epithelial tissue was present. C, *T* = 8 weeks. Complete healing occurred by week 9 with no recurrence.

Figure 2.
CASE STUDY 2: VENOUS ULCER ON THE ANKLE OF A DIABETIC PATIENT



A, *T* = 0 weeks. Patient had history of diabetes mellitus, congestive heart failure, and edema. Prior treatments included compression, debridement, oxidized regenerated cellulose, silver collagen, and steroid therapy. B, *T* = 7 weeks. Wound was granulated and epithelializing. C, *T* = 11 weeks. One week after complete healing.

Table 6.

CLINICAL IMPRESSIONS REGARDING USE OF OFM

Well-tolerated by patients and does not need to be removed at dressing change
Robust handling characteristics, quick rehydration, conforms well to underlying wound bed and adheres within 2–3 d
No suturing required, allowing application by a wide range of wound care practitioners
Available off-the-shelf, no special storage requirements, and 3-year shelf life
Available in large sizes (up to 400 cm^2)

of 64.5% at 12 weeks. The authors' current findings are promising and suggest OFM may assist closure of chronic wounds. Table 6 illustrates the clinical impressions regarding the use of OFM. A large, comparative clinical study is warranted. ●

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Leg Ulcer Treatment Outcomes with New Ovine Collagen Extracellular Matrix Dressing: A Retrospective Case Series

Gregory A. Bohn, MD, FACS; and Kimberly Gass, RN

ABSTRACT

The purpose of this study was to describe the rate of closure observed in venous leg ulcers during treatment with ovine collagen extracellular matrix dressings and compression. Fourteen patients with 23 wounds were retrospectively evaluated with respect to healing rates, time to closure, and weekly facility charge fees.

KEYWORDS: ovine collagen extracellular matrix, wound care dressing, venous leg ulcer

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INTRODUCTION

Venous leg ulcers (VLUs) account for up to 80% of lower-extremity ulcers in the United States[1] and are commonly associated with pain, itching, altered appearance, loss of sleep, substantial disability, social isolation, depression, and disappointment in treatment.[2–4] Treatment costs for VLUs, which are directly associated with time to achieve complete closure, can average more $4000 per month and between $16,000 and $40,000 per treatment episode.[4–6] Despite renewed focus on prevention and treatment, an estimated 3 million Americans are currently living with a VLU,[7] amounting to an estimated $1.9 to $2.5 billion in annual healthcare costs.[8] These costs do not include the financial toll imposed by VLU-related limitations on mobility and work capacity, patient out-of-pocket expenses, and psychological effects.

In addition to underlying venous insufficiency, elevated matrix metalloproteinase (MMP) levels play a major role in the pathophysiology of VLUs, contributing to disruption or damage of the extracellular matrix (ECM).[9,10] Compression therapy is considered a standard management strategy for venous ulcers; its positive effect on venous ulcers is clearly supported by a large body of evidence.[11] Yet, compression therapy in itself is often insufficient to heal the wound within an acceptable timeframe.[4] For example, with compression only, complete VLU closure rates of 50% to 65% at 6 months have been reported.[12–14] Approximately 20% remain unhealed at 2 years, and approximately 8% remain unhealed at 5 years.[15]

Although general superiority of 1 dressing over another in treating venous ulcers has not been demonstrated in the literature,[16] recent studies have identified the role of collagen-based ECM dressings in improving wound healing by reducing inflammatory mediators.[17–19] Use of decellularized ECM-based products in a variety of applications has increased during recent years because of the relatively rapid vascularization of these biomaterials, generally leading to improved healing outcomes.[20–22] Collagen matrices restore balance at the microenvironment level through binding and inactivation of excess MMPs while providing moist wound healing and protecting the biologic activity of endogenous growth factors.[23,24] Intact collagen ECM (CECM) dressings allow structural support for tissue regeneration, as well as provide cytokines and growth factors in physiologic concentrations.[25]

An established regimen of treatment using compression and collagen dressings has been shown to be effective in improving outcomes and healing in venous ulcers.[23,26] However, most collagen dressings are effective for up to 72 hours and require dressing plus compression changes every 3 to 4 days.[18,23]

A new ovine-based CECM dressing (Endoform dermal template; Mesynthes Ltd, Wellington, New Zealand; distributed by Hollister Incorporated, Libertyville, Illinois) has recently been cleared by the Food and Drug Administration for use in dermal applications, including treatment of chronic and acute wounds. The dressing is prepared from propria submucosa of ovine forestomach tissue using processes to delaminate and decellularize the tissue.[27,28] The CECM dressing contains 90% natural, intact collagen and 10% secondary ECM components. This collagen dressing is effective up to 7 days, which may translate into cost savings, versus traditional collagen dressings that typically require twice-weekly dressing changes.

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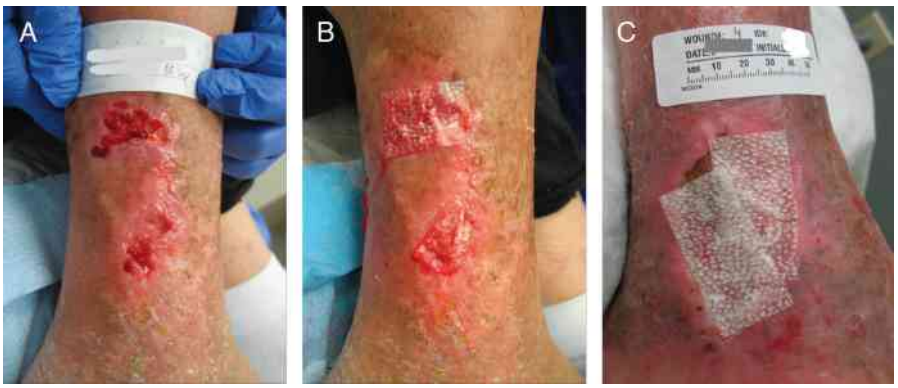
Figure 1A–C.
CECM DRESSING APPLICATION



A, Wound bed is prepared, including sharp debridement and irrigation, prior to CECM dressing application. B, Collagen ECM dressing may be cut to fit the wound dimensions or may overlap the wound edges. C, Collagen ECM dressing is hydrated with sterile saline prior to application of cover and compression.

The purpose of this study was to describe wound closure outcomes in VLUs during treatment with CECM dressing. Clinic records of patients with VLUs treated with CECM dressings were retrospectively reviewed to determine rate of wound healing, days to wound healing, and number of weeks in care.

METHODS

A retrospective review was conducted of medical records of consecutive patients who were treated with CECM dressing. Approval for this study was granted by the clinic's institutional review board. Outpatients 18 years or older with at least 1 venous ulcer treated with CECM dressings in the clinic between February 1, 2012, and December 31, 2012, were included in the analysis.

The CECM dressing was applied according to instructions for use by a team of clinicians (Figure 1A–C). Excisional debridement was performed at the initial dressing placement, and selective sharp debridement was subsequently performed as needed (Table 1). Using aseptic technique, a dry sheet of CECM dressing just larger than the ulcer was trimmed to overlap wound margins and placed on the wound bed. The CECM dressing was hydrated with sterile saline as outlined in the instructions for use. Light pressure was applied to the dressing to ensure it conformed to the underlying wound bed.

A sheet of petroleum jelly gauze was applied over the CECM, followed by 10 × 10-cm secondary gauze dressing, rolled gauze if needed, then the compression system. The number of patient wounds that received each of various compression systems is listed in Table 1. Each patient was followed up twice weekly: 1 nursing clinic visit on day 3 and 1 physician clinic visit on day 7. At the nursing visit on day 3, the compression wrap and dressing cover were changed, and the CECM dressing remained in place. At the physician clinic visit on day 7, debridement was performed if needed, and CECM dressing and compression were reapplied. Application of CECM dressings was discontinued when the wound was re-epithelialized.

Charts were reviewed for patient demographics, wound dimensions, total treatment time, number of weeks to heal, and current procedural terminology charges. Data were deidentified and imported into a Microsoft Excel spreadsheet. Data analysis was performed with SAS Software version 9.0 (Cary, North Carolina).

Table 1.

TYPES OF DEBRIDEMENT AND COMPRESSION USED DURING THE STUDY PERIOD

Wound Therapies	n (Patient Wounds)	%
Debridement		
Excisional debridement	23	100
Selective sharp debridement	9	39.1
Compression		
3-layer compression wrap	12	52.2
4-layer compression wrap	14	60.9
Self-adherent 2-layer wrap	10	43.5
Self-adherent, light 2-layer wrap	1	4.3
Single-layer, long-stretch wrap	1	4.3
Elasticated tubular bandage	1	4.3
Zinc oxide/calamine–impregnated gauze	2	8.6

RESULTS

Data from 14 patients with 23 VLUs treated with CECM dressings were analyzed. Ten of the patients were men (71.4%); the average patient age was 55.3 years (range, 37–78 years). Demographic and outcomes data are detailed in Table 2. The average surface area at CECM dressing initiation was 3.7 cm^2 (range, 0.2–23.4 cm^2). A total of 23 of 23 wounds (100.0%) healed during the study timeframe with CECM dressings during an average of 7.3 weeks (range, 2–15 weeks). One wound (10A) was treated with CECM dressings for 4 weeks until the surface area was 0.06 cm^2, at which time the investigator determined that CECM dressings could be discontinued. Wound 10A healed spontaneously, whereas wound 10B on the same patient continued to receive CECM dressing applications.

Of the 23 wounds that healed, 22 (95.7%) were healed within 12 weeks. Wound 10B was healed at 15 weeks. Total number of wounds open/closed per week is charted in Figure 2. Wound 12C was completely closed at week 11, but the ulcer reopened the following week, then was closed again on week 14. All other ulcers remained closed during short-term follow-up.

Average surface area reduction of all wounds was 97.9% at 12 weeks. Wounds healed at an average rate of 0.88 cm^2 (range, -0.1 to 11.7 cm^2) per week. A life table method survival analysis (SAS proc lifetest method = lt) indicated that 50% of wounds treated with CECM were closed by 7 to 8 weeks. There were no adverse effects or events associated with CECM reported in any of the patients during the study.

According to the hospital chargemaster committee, an average facility fee of $233.50 was charged at the midweek (day 3 or 4) visit for nursing compression wrap and dressing cover change. Dressing supply and application costs were bundled within this charge. This midweek visit was a nurse visit, not a physician visit, and therefore, no professional fee was charged.

PATIENT CASE STUDY

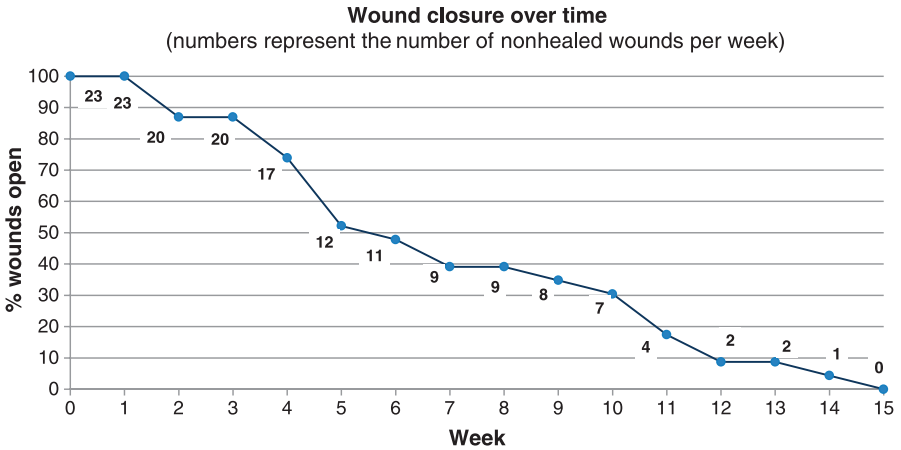
A 68-year-old man with a 20-year history of venous stasis and recurrent venous ulceration presented with a venous ulcer on the right medial malleolus. The patient was obese with history negative for diabetes and vascular disease. His ankle-brachial index was 0.93 on the left and 0.90 on the right. He had a history of bilateral vein stripping, used compression, and had been evaluated for subfascial ligation of perforators, but declined the operation. The patient returned to the clinic every 8 to 9 months with recurrent ulceration despite adequate stocking compression (30–40 mm Hg). This venous ulcer had been present for 7 months despite treatment and compression. The wound had previously been treated unsuccessfully with bilayered, bioengineered skin substitute (3 times)

Table 2.

PATIENT DEMOGRAPHICS

n	Patient/Wound ID	Baseline Area at Initial OCM Dressing Application, cm^2	Duration of OCM Dressing Treatment, wk	Wound Size End of OCM Dressing Treatment, cm^2	Healing Rate During OCM Dressing, cm^2/wk	Wound Size Reduction at Closure or 12 wk, Whichever Is Sooner, %
1	3	3.0	7	0.0	0.28	100
2	4	0.7	4	0.0	0.18	100
3	5A	4.4	9	0.0	0.41	100
4	5B	0.7	5	0.0	0.09	100
5	6A	0.6	11	0.0	0.06	100
6	6B	18.6	11	0.0	2.04	100
7	7	0.5	5	0.0	0.12	100
8	8A	0.8	2	0.0	0.41	100
9	8B	0.2	2	0.0	0.09	100
10	9A	0.8	5	0.0	0.09	100
11	9B	4.2	11	0.0	0.38	100
12	10A	0.3	4	0.06	0.06	100
13	10B	1.7	15	0.0	0.09	51.5
14	11	23.4	2	0.0	11.70	100
15	12A	1.0	5	0.0	0.21	100
16	12B	0.3	12	0.0	−0.11	100
17	12C	9.3	14	0.0	0.98	100
18	12D	0.5	5	0.0	−0.13	100
19	13	5.0	12	0.0	0.46	100
20	14A	5.7	4	0.0	1.82	100
21	14B	1.8	7	0.0	0.26	100
22	15	0.8	6	0.0	0.10	100
23	16	0.8	10	0.0	0.07	100
Average		3.7	7.3		0.9	97.9
SD		6.0	4.0		2.4	10.1
Range		0.2–23.4	2–15		−0.13 to 11.7	51.5–100

Figure 2.
NUMBER OF OPEN WOUNDS BY WEEK

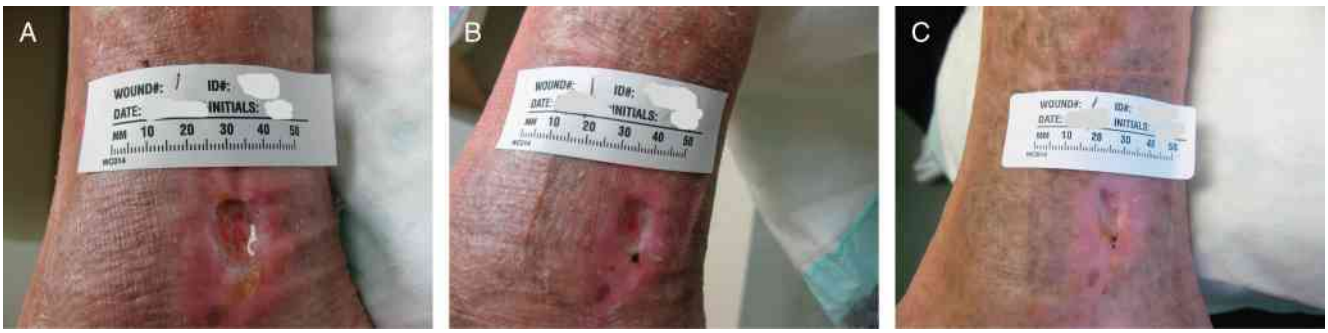


and a collagen matrix graft. Following good wound bed preparation, a CECM dressing was applied (Figure 3A). After 5 applications of CECM dressings, the wound was considerably decreased in size and re-epithelializing from the wound edges (Figure 3B). At 12 weeks, the ulcer was closed (Figure 3C).

DISCUSSION

The positive effects of CECM dressings in treating VLUs were demonstrated in this case series through a high percentage of wounds that were closed within 12 weeks (22/23; 95.7%). Larger, prospective studies report lower percentage rates of wound closure with other collagen dressings at 12 weeks. In 1 interim analysis of 84 VLUs, healing rate at 12 weeks was 71% with pig small-intestine submucosa and 46% with standard care.[29] In a different study, results at the end of the 12-week treatment period showed that healing occurred in 55% (34/62) of patients who received small-intestine submucosa wound matrix plus standard care versus 34% (20/58) of patients who received compression only (P = .0196).[30]

Figure 3A–C.
VENOUS ULCER CASE
A, DAY 0
B, WEEK 5
C, WEEK 12



Chronic, edematous venous leg ulcer with raised wound edges after 7 months of advanced wound care, including 3 applications of bilayered bioengineered skin substitute and a collagen matrix graft. Following good wound bed preparation, CECM dressing is applied.

In a study of VLUs, a total of 15 of 37 ulcers (41%) treated with collagen and oxidized regenerated cellulose healed in 12 weeks, versus 11 of 36 (31%) with Adaptic (Medline, Mundelein, Illinois).[18]

The calculated closure rate of 0.88 cm^2/wk may have been skewed with inclusion of wound 11, which displayed a rapid healing response. One week prior to CECM initiation, wound 11 measured 41.0 cm^2, and at first CECM application, the wound measured 23.4 cm^2. After 2 weeks of CECM dressings, the wound was completely closed. Excluding wound 11 from the data set produced an average healing rate of 0.44 cm^2, a rate that may be more representative of the study population.

Although compression wrap and dressing cover were changed twice per week during the study period for frequent wound observation, CECM dressings may be used up to 7 days, and compression wrap change frequency would typically be reduced to once weekly (in tandem with CECM dressing changes). Compared with other collagen dressings requiring at least twice-weekly application, the once-weekly application of CECM dressings saves healthcare system dollars in terms of reduced facility fees, material costs, and home nursing visits. Although the second weekly visit is a nursing visit versus a physician visit, it still requires the collagen, a 2- or 4-layer wrap, and the nurse's time. Based on average facility fees the investigators' institution billed during the study period, negating a midweek visit to the clinic for the purpose of changing the collagen dressing could yield a per-patient healthcare cost savings of up to $233.50 per week.

Favorable healing rates of CECM dressings may be related to the biomaterial's intact, nonreconstituted matrix. Structural studies have shown that CECM biomaterial is relatively strong and elastic and retains the complex collagen architecture of native tissue ECM.[31,32] Structural components include elastin, fibronectin, and glycosaminoglycans.[32] The CECM has been shown to retain secondary ECM-associated molecules, including fibroblast growth factor 2, heparin sulfate, and hyaluronic acid, as well as remnant basement membrane components associated with forestomach luminal surface and endothelial basement membranes.[32]

High levels of various MMPs are consistently reported in chronic wounds.[33,34] These proteases sequentially break down native extracellular matrices, causing a weakened molecular environment in the wound because of the damaged essential proteins for healing. Specifically, in a study of fluids and tissues of healing and nonhealing ulcers, Nwomeh et al[35] found that neutrophil-derived MMP-8 is the predominant collagenase present in normal healing wounds; results of that study suggest that overexpression and activation of collagenase MMP-8 is likely involved in the pathogenesis of nonhealing chronic ulcers.[35]

The CECM biomaterial appears to have an effect on MMP levels.[27] In a scientific solid-state assay study, Negron et al[27] showed that in the presence of intact CECM, residual activity of MMP-8 was reduced relative to untreated control at all time points and displayed a decrease in activity over time. In the same study, extracts of CECM were shown to inhibit a broad spectrum of excess MMPs, particularly collagenases, gelatinases, and neutrophil elastases.[27]

In the investigators' experience, CECM dressing technology has several advantages in practice. The matrix dressing does not require fixation and can be applied by any clinician in any care setting or by patients at home. It is a relatively large, thick, dense material that stabilizes easily over the wound. Generally, payer plans reimburse for advanced wound care matrices over a VLU only after the VLU has failed to adequately respond to 2 months of conservative treatment with compression therapy alone.[36,37] This ovine CECM dressing differs from that model as it is classified for reimbursement as a collagen dressing as opposed to an advanced wound care matrix dressing. As such, it is relatively inexpensive ($10–$12 each) and can be applied from the initial visit.

Investigators in the authors' clinic have switched to the CECM dressing as the standard venous ulcer dressing under compression because of its versatility, relatively low cost, and perceived effectiveness. Use of this dressing has reduced clinic applications of collagen dressings by 50%, and because this matrix collagen dressing is priced at the low end of collagen dressings, expenditure per collagen dressing has been reduced at the authors' clinic.

Because this advanced ECM dressing can be initiated during what is typically considered the 8-week timeframe of conservative treatment, based on local coverage determination policy, clinicians and patients can get a head start in wound healing with this dressing. Since the conclusion of the study, overall faster wound healing times have been observed, compared with prior treatment regimens. Use of this CECM dressing in clinic has reduced the number of outlier ulcers, that is, ulcers that extend beyond a 12-week healing window. Patients prefer CECM dressings compared with previous collagen dressings because of reduced dressing change frequency, perceived faster healing, and fewer out-of-pocket expenses for dressings. Reduced dressing application frequency may improve patient compliance with therapy by minimizing transport and time inconveniences related to clinic visits.

Indications for CECM dressings are listed in Table 3. According to manufacturer recommendations, CECM dressings are not for infected wounds or full-thickness burns and should not be used on patients with known sensitivity to ovine material. Precautions should be taken in cases of acute inflammation and excessive exudate or bleeding.

To date, the authors believe this is the first case series evaluating the use of CECM exclusively in VLUs. Liden and May[38] evaluated the matrix dressing in a series of 19 patients with 24 wounds of various etiologies, including venous, diabetic, and

Table 3.

INDICATIONS FOR OCM DRESSINGS

Pressure ulcers
Venous ulcers
Diabetic ulcers
Chronic vascular ulcers
Tunneled/undermined wounds
Surgical wounds (donor sites, grafts, post–Mohs surgery, post–laser surgery, podiatric, and wound dehiscence)
Traumatic wounds (abrasions, lacerations, partial- and full-thickness burns, and skin tears)
Draining wounds

incisional wounds.[38] The authors reported 50% of wounds closed at 12 weeks; average surface area reduction of all wounds at 12 weeks was 73.4%.[38]

CONCLUSIONS

Preliminary results of this retrospective data analysis suggest that the use of CECM dressings in VLUs may lead to improved healing, as well as potential cost savings. This study, however, has all of the limitations of a retrospective, nonrandomized, noncontrolled study. Because all wounds were treated with CECM dressings, it is not possible from the data to understand the full impact of CECM dressings versus alternative treatments. In addition, there could be a carryover effect for those who were initially treated with other dressings at baseline before crossing over to CECM dressing treatment. Wound duration and prior treatments were not considered in the data, potentially confounding study results. Investigator bias may also have confounded the results of this study with respect to wound selection and, in some cases, timing of switchover to CECM dressings.

Large, prospective, controlled trials are needed to help delineate the effectiveness of this new CECM dressing in treating VLUs and other wound types. In particular, a randomized, prospective study of consecutive VLU patients treated with compression and CECM dressings versus cellulose collagen dressings (12–16 weeks) could provide needed comparative evidence, as well as enhanced validity and generalizability of study results. A priori power analysis should be used in future CECM dressing studies to accurately estimate sufficient sample size to achieve adequate power. ●

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Use of Collagen Extracellular Matrix Dressing for the Treatment of a Recurrent Venous Ulcer in a 52-Year-Old Patient

Arturo González

ABSTRACT

CASE: This case study describes treatment for a 52-year-old man with a recurrent venous leg ulcer using a collagen dressing with extracellular matrix.

BACKGROUND: The patient was admitted to the wound care service for a 3-week-old recurrent venous ulcer. Treatment included application of a collagen dressing with extracellular matrix twice weekly or as needed by the patient; application of a secondary dressing (4 × 4 gauze); and coverage with an expandable netting or gauze using a conforming stretch gauze bandage and latex-free dressing retention tape.

CONCLUSION: The initial venous leg ulcer in this patient required 10 weeks to achieve closure. Ninety-eight percent resolution of the recurrent ulcer had occurred within 4 weeks of treatment, with complete closure at 7 weeks. The average healing time for recurrent venous ulcers is reported in the literature to be longer than initial venous ulcers. In the case provided, collagen ECM dressings promoted complete wound healing in 49 days.

KEY WORDS: Chronic wound healing, ECM dressings, Extracellular matrix (ECM), Venous leg ulcers, wound reoccurance

INTRODUCTION

Venous leg ulcers occur in patients who experience chronic venous insufficiency; they are one of the most common chronic wounds seen in clinical practice. It is estimated that approximately 1 million patients in the United States currently have this condition.[1] While the treatment of venous leg ulcers requires intervention to address the underlying cause of the disease, direct care of the ulcer must also be considered.[2] Venous leg ulcers have a high rate of recurrence that negatively influences health-related quality of life and the provider's ability to enhance patient outcomes.[2] Efforts to reduce recurrence have typically focused on patient education to facilitate changes in lifestyle.[3] The use of compression hosiery, increased physical activity, and leg elevation are recommended for preventing recurrence.[3] Even when patients engage in these self-care activities, recurrence of the venous ulcer may still result.[3]

Compression is essential for wound in patients with venous leg ulcers.[1,2] Various proprietary, adjustable compression boots and bandage systems have been developed to facilitate wound healing and prevent recurrence.[4] However, a systematic review comparing boot and bandage systems found no difference in wound-healing rates.[4] Recurrent venous ulcers are especially difficult to treat because most recurrent wounds represent significant changes in skin tissue that may not respond to conventional treatment.[5] Significant degradation of the extracellular matrix (ECM), which is vital to the healing process, may occur when a venous leg ulcer occurs.[5] Therefore, effective treatment of a recurrent venous ulcer may require additional interventions to help address these issues and restore skin integrity. Mostow and colleagues[6] completed a randomized controlled trial that compared compression therapy alone with compression therapy plus a collagen dressing with porcine-based ECM in 120 patients with at least 1 venous leg ulcer. They reported that patients treated with compression plus the extracellular graft matrix were more likely to heal within a 6-month treatment period than were subjects managed with compression therapy alone. They further reported outcomes at 6 months following the original protocol-driven treatment. Fifty-four subjects (45% of the original study sample) were evaluated; none of the patients treated with combination therapy experienced a recurrent ulcer as compared to a 30% recurrence rate in patients treated with compression therapy alone.

Current efforts to improve chronic wound healing and prevent the recurrence of venous ulcers have concentrated on the delivery of ECM components directly to the wound site via various bandage systems.[5] Research regarding the use of ECM components in various bandage systems has demonstrated that this approach can be effective in healing chronic and recurrent wounds.[7,8] Although the specific mechanism by which this process occurs is not fully understood, it is believed that ECM components, when delivered to the wound site, can provide a temporary scaffold enabling the body's natural healing systems to work more effectively.[5] Once the healing is initiated, the patient's body is able to sustain the process, allowing for more rapid wound healing. Enhanced healing may reduce the likelihood of recurrence by creating a stronger tissue barrier to protect against the redevelopment of the wound over time.[6]

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The author declares no conflicts of interest.

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Based on this knowledge, I elected to treat a patient with a recurrent venous leg ulcer and chronic venous insufficiency with a collagen-based dressing with ECM in an effort to enhance wound healing and prevent additional recurrences.

Case History

Mr H., a 52-year-old man, was first evaluated by our wound care team for treatment of a venous leg ulcer located on the left, medial ankle. Treatment of the initial wound occurred between November 6, 2003, and February 9, 2004. Management included cleansing with a saline-based wound cleanser and silver-releasing foam dressing (Restore wound cleanser, Hollister, Libertyville, Illinois; Contreet/Biatain Ag Foam Antimicrobial Barrier Dressing with Silver, Coloplast, Minneapolis, Minnesota). The use of adhesives was minimized, and we recommended the use of an expandable netting or gauze Unna Boot for compression. The patient was discharged from care in February with complete ulcer healing. Recommendations for lifestyle changes were made to help reduce recurrence, such as compression therapy, exercise, and leg elevation.

Mr H. remained ulcer free for 9 years when he was referred for treatment of a recurrent venous ulcer on the left, medial ankle. At that time, the patient indicated he had been compliant with compression therapy until 6 months prior to the development of the current wound. At this time, he stopped the use of compression therapy when a change in insurance coverage resulted in elimination of coverage for compression stockings. As a result, he was unable to continue compression therapy.

Current Treatment

At the time of admission to our home care wound service, his wound was 3 weeks old. The patient lived at home with his wife and was alert, oriented, and independent in ambulation and activities of daily living. His medical history included hyperlipidemia, hypertension, and type 2 diabetes mellitus. He did not perform home blood glucose monitoring; however, a recent hemoglobin A_{1c} level was 7.5%. Medications at that time were metformin, furosemide, simvastatin, losartan, and amlodipine. His past surgical history included shoulder replacement and wrist reconstruction secondary to a fall.

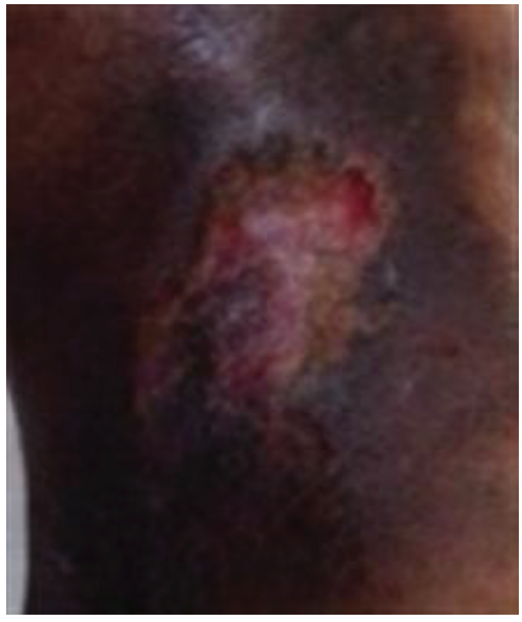

Figure 1. Wound at the initiation of treatment: August 5, 2013: length, 4.0 cm; width, 4.5 cm; and depth, 0.1 cm.

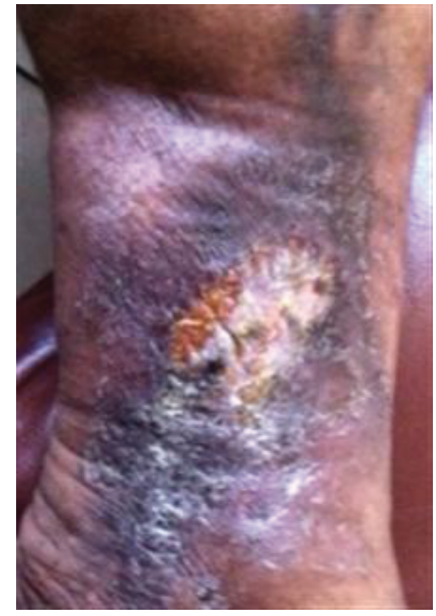

Figure 2. Wound at the middle of treatment: August 19, 2013: length, 3.4 cm; width, 3.3 cm; and depth, 0.1 cm.

Initial evaluation revealed a venous lug ulcer that was 4.0 cm in length by 4.5 cm in width; the ulcer was 0.1 cm in depth (Figure 1). Topical treatment of the venous leg ulcer included a collagen dressing with ECM (Endoform, Hollister Wound Care Libertyville, Illinois). The dressing was applied twice weekly or as needed by the patient; application of a secondary dressing (4 × 4 gauze); and expandable netting or gauze using conforming stretch gauze bandage (McKesson Tubular Elastic dressing retainer size 6). This did not produce the therapeutic level of compression, therefore we added a cohesive bandage 4 in × 5 yards and latex-free dressing retention tape (Coban, 3M, St Paul, Minnesota). Collagen ECM dressings are formulated with a 90% collagen base and 10% ECM component

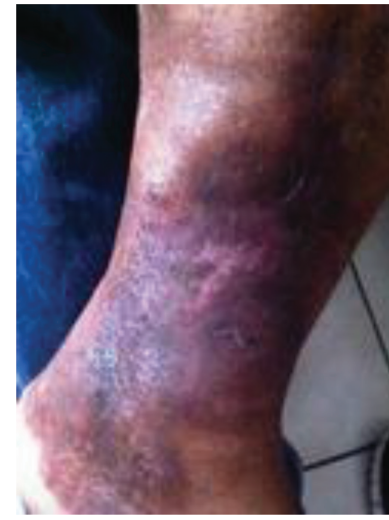

Figure 3. Wound at the completion of treatment: September 23, 2013 (resolved): length, 0 cm; width, 0 cm; and depth, 0 cm.

designed to repair missing or degraded ECM at the wound site.[9] The patient's wound was assessed 2 weeks later; the wound was 3.4 cm in length, 3.3 cm wide, and its depth was 0.1 (Figure 2). Ten days later, the wound size had shrunk approximately 98%.

The patient was reevaluated after 7 weeks of therapy. This lapse in visits occurred because of a change in primary care physician, resulting in the absence of authorization for additional wound care visits. Nevertheless, when the patient was examined after 7 weeks, we found that the wound had closed and complete epithelialization had occurred (Figure 3). Mr H. reported that he had continued the topical therapy we proscribed and adhered to compression therapy during this period of time. He was discharged from care with recommendations for continued use of compression stockings to prevent the recurrence of the ulcer. The time for wound healing for this recurrent venous leg ulcer was 7 weeks as compared to 10 weeks for the initial venous ulcer.

DISCUSSION

Venous leg ulcers are a common and debilitating condition associated with a chronic underlying disease, chronic venous insufficiency.[10] The condition is often conceptualized as occurring in a "forever healing" cycle; venous leg ulcers require weeks to months to heal, and recurrence rates are as high as 70%.[10] Even patients who regularly adhere to preventive interventions such as the regular and consistent use of compression hosiery experience recurrence rates as high as 60%.[10] Research suggests that the average time to heal a first-time venous leg ulcer is 80 days, while a recurrent venous ulcer requires a mean time of 117 days to heal.[11] Therefore, treatment must be based on healing the current ulcer, preventing its recurrence whenever possible, and providing treatments that may facilitate healing if a recurrent wound develops. Materials designed to replace the ECM of the skin have been shown to promote wound healing in patients with nonhealing wounds, along with the use of compression.[12,13]

In this case, treatment of a recurrent venous leg ulcer resulted in faster healing time (7 weeks) than did treatment of the initial wound (10 weeks), and he achieved 98% wound closure within the first month of treatment. While it is not possible to generalize these findings, the success of the collagen ECM dressing in treating this patient indicates the need for further investigation of the role of ECM in management of recurrent venous leg ulcers.

CONCLUSION

Venous leg ulcers tend to heal slowly and, even with the consistent use of compression hosiery and lifestyle changes, likely to recur. Recurrent venous ulcers tend to heal even more slowly than the original ulcer. I described the case of a 52-year-old male patient with a recurrent venous leg ulcer treatment with compression and a collagen dressing with ECM. Healing time for the patient's recurrent venous ulcer was shorter than the time required to heal his initial venous ulcer. It was also shorter than the average healing time reported in the literature.[11] Additional research is needed to more fully evaluate the role of collagen dressings with ECM in the management of initial and recurrent venous leg ulcers in patients with chronic venous insufficiency.

KEY POINTS

- Venous leg ulcers in patients with chronic venous insufficiency recur in up to 70% of patients who experience an initial ulcer and as many as 60% who adhere to regimen of preventive interventions including compression.
- Recurrent venous ulcers tend to require more time to heal than does an initial ulcer.
- Use of a collagen-based dressing with ECM led to more rapid closure of a recurrent venous leg ulcer in a 52-year-old man than did healing of the initial ulcer.

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Use of Ovine-based Collagen Extracellular Matrix and Gentian Violet/Methylene Blue Antibacterial Foam Dressings to Help Improve Clinical Outcomes in Lower Extremity Wounds: A Retrospective Cohort Study

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Abstract: Dressings that provide broad spectrum metalloprotease reduction along with inherent aspects of an extracellular matrix may contribute to improved wound healing outcomes and shorter treatment times. *Objective.* The author performed a retrospective case series analysis to determine the clinical outcomes of regular debridement with the use of ovine-based collagen extracellular matrix dressings and gentian violet/methylene blue polyurethane antibacterial foam dressings in treating 53 patients with 53 chronic lower extremity wounds (diabetic foot ulcers [DFUs], venous leg ulcers, and heel pressure ulcers). *Materials and Methods.* Patients were treated twice weekly in an outpatient clinic for the first 4 weeks and weekly thereafter until closure. *Results.* Average body mass index (BMI) for the study population was 28.3, and the average patient age was 75.9 years. Mean percent wound surface area reduction at 4, 8, and 12 weeks was 38.5%, 73.3%, and 91.3%, respectively. Average time to closure for all wounds was 10.6 weeks (range, 5–24 weeks). All wounds were 100% reepithelialized by week 20 except 1 DFU that reepithelialized at week 24. The average cost of care for a single wound episode (from presentation to closure) was $2749.49. *Conclusion.* Results of this analysis showed that the healing of chronic wounds in this series could be achieved at a reasonable cost with regular debridement and a collagen matrix dressing regimen, even in patients of advanced age and above average BMI as well as in wounds that did not achieve > 40% wound surface area reduction at 4 weeks.

Key words: antibacterial foam dressings, collagen extracellular matrix dressing, gentian violet/methylene blue, MMP reduction, ovine-based

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Chronic lower extremity wounds are a significant cause of morbidity and a drain on health care resources worldwide as an increasingly prevalent and complex condition to treat. In the United States alone, chronic lower extremity ulcers affect an estimated 2.4 to 4.5 million people.[1] Treatment costs for a venous leg ulcer (VLU) have been estimated at about $4000 per month and $16 000 per treatment episode,[2] and recent research[3] suggests an annual US payer burden of $14.9 billion. Diabetic foot ulcer (DFU) care adds between

$9 billion to $13 billion to direct annual US government and private insurer costs associated with diabetes itself.[4]

Following holistic fundamentals of good clinical wound care is essential in successful management of chronic wounds and includes addressing factors such as systemic diseases, medications, offloading, nutrition, and tissue perfusion/oxygenation.[5] Patient comorbid conditions, such as diabetes, renal failure, peripheral vascular disease, and smoking, can greatly influence healing[6]; these conditions must be addressed to correct causes of tissue damage. A basic understanding of the pathological condition of a chronic wound is important in addressing cost and patient needs as well.

In addition to underlying medical conditions, chronic wounds are characterized by a complex etiology that can include abnormal cell-extracellular matrix (ECM) interactions, imbalances of matrix metalloproteinases (MMPs), elevated bioburden levels and bacterial biofilm, and a prolonged inflammatory response — all of which can damage the wound ECM.[7] While MMPs are essential in normal healing, elevated MMP levels have been linked to wound failure.[7,8] Elevated protease activity in a wound can break down the vital matrix and interfere with or change cell signaling.[9,10]

A collagen dressing with a preserved structural component can serve as a provisional ECM dermal template and guide cellular interaction necessary to prompt keratinocyte migration.[11] Dressings that provide broad spectrum MMP reduction, along with the inherent aspects of an ECM, may contribute to improved wound healing outcomes and shorter treatment times.[8] Preliminary reports of an ovine-based collagen extracellular matrix (CECM) dressing (Endoform Dermal Template; Hollister Wound Care, Inc, Libertyville, IL) demonstrated the benefits in chronic wound healing.[12-14] Ovine-based collagen extracellular matrix dressings are comprised of collagens I, III, and IV; they have been shown to retain the complex collagen architecture of native tissue ECM as well as ECM-associated secondary molecules including laminin, fibronectin, and glycosaminoglycans.[15] The dressing has been shown in vitro to have buffering capacity for collagenases MMP-1, MMP-8, and MMP-13; stromelysins MMP-3 and MMP-10; MMP-12 and MMP-14; gelatinases MMP-2 and MMP-9; and neutrophil elastase.[16] This broad spectrum of MMP inhibition may help protect against other detrimental MMP activity in the chronic wound microenvironment.

The purpose of this study was to analyze the clinical outcomes with the use of CECM dressings and gentian violet/methylene blue (GV/MB) antibacterial polyurethane (PU) foam (Hydrofera Blue; Hollister Wound Care, Inc, Libertyville, IL) dressings in treating chronic lower extremity wounds. The primary endpoint analyzed was mean percent wound surface area reduction at 4 weeks, and the secondary endpoint of the analysis was time to wound closure. Average treatment costs were also included in the analysis.

Table 1. Patient demographics

	N	%	Avg	SD	Range
Patients	53				
Men	22	41.5			
Women	31	58.5			
Age (y)			75.9	12.4	33–101
BMI			28.3	5.1	17.4–43.3
Wounds treated	53				
Wound area at presentation (cm^2)			5.8	7.4	1.2–47.5

Avg: average; SD: standard deviation; BMI: body mass index

Materials and Methods

A retrospective case series analysis of observational, longitudinal data collected from a single center was performed by a single investigator. Midlands Independent Institutional Review Board (IRB) reviewed this study and exempted it from IRB review under the Basic Health and Human Services Policy for Protection of Human Research Subjects (45 CFR §46). Records of patients with chronic full-thickness lower extremity ulcers (DFUs, VLUs, and pressure ulcers) that received treatment with CECM and GV/MB antibacterial PU foam dressings in an outpatient setting at the West Boca Center for Wound Healing in Boca Raton, Florida, between January 1, 2014, and January 31, 2015, were included in the analysis. Chronic was defined as a non-progressing wound of at least 4 weeks in duration.

All patients were treated twice weekly in the clinic for the first 4 weeks, and all wounds were treated in the following similar manner. During the initial visit, all patients completed a peripheral arterial disease screening questionnaire, which qualified or disqualified the need for vascular testing. Patients who underwent noninvasive arterial vascular testing, which showed an abnormal ankle brachial index and subtherapeutic skin perfusion pressure (< 50 mm Hg), were referred to vas-

cular surgery for evaluation and potential intervention. Following adequate patient preparation, wounds were cleansed with saline or dermal cleanser and sharp surgical debridment as needed. Digital planimetry was not available at the treatment location, so basic linear measurements were used to calculate the wound area. Dimensions were recorded for length and width of each wound measured at the widest and longest points. A CECM dressing was hydrated with sterile saline and placed on the wound. A GV/MB antibacterial PU foam dressing was applied over the CECM dressing, followed by a secondary gauze dressing, and rolled gauze and/or compression as needed. Diabetic foot ulcers were offloaded as appropriate.

At the mid-week appointment, wounds were again cleansed and examined, but not surgically debrided. A new CECM dressing was applied when there was no visible evidence of the previous CECM dressing in the wound bed. After the initial 4-week period, patients received 1 weekly treatment consisting of cleansing, surgical debridement (as needed), application of CECM and GV/MB antibacterial PU foam dressings, and compression if appropriate until the wound closed.

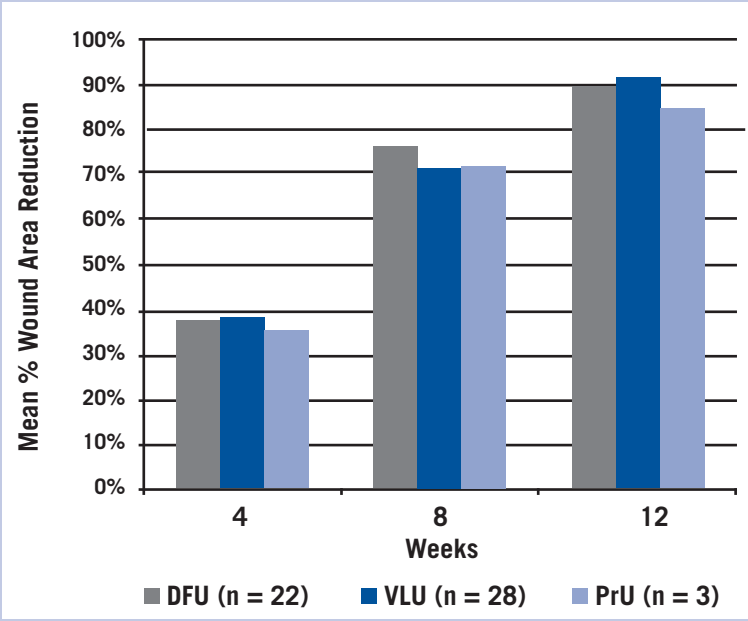

Figure 1. Wound surface area reduction at weeks 4, 8, and 12.
DFU: diabetic foot ulcer; VLU: venous leg ulcer; PrU: pressure ulcer

Cost formula. Average cost per week during the first 4 weeks was calculated as per the following formula:

> Cost per week = average charge for first evaluation and management (E/M Level 3) visit ($74.75) + debridement (97597) charge ($91.00) + average cost of CECM dressing ($11.50) + average cost of GV/MB antibacterial PU foam dressing ($6.50) + average charge for second E/M Level 3 visit ($74.75) + average cost of CECM dressing ($11.50) + average cost of GV/MB antibacterial PU foam dressing ($6.50) = $276.50.

Average cost per week during the subsequent weeks until wound closure (weeks 5–24) was calculated per the following formula:

> Weeks 5–24 = average charge for E/M Level 3 ($74.75) or surigcal debridement (97597) ($91.00) + average cost of CECM dressing ($11.50) + average cost of GV/MB antibacterial PU foam dressing ($6.50) = $92.75 (E/M Level 3) and $109 (surgical debridement).

Results

In this case series, 53 patients with 53 wounds were treated. Of those, 31 (58.5%) were women and 22 men. The types of wounds treated were DFUs (n = 22), VLUs (n = 28), and pressure ulcers (n = 3). Average body mass index (BMI) of the study population was 28.3; average patient age was 75.9 years. The average wound surface area at first CECM dressing application was 5.8 cm^2. Patient demographics are presented in Table 1.

After 4 weeks, the average wound surface area was 3.47 cm^2 and mean percent wound surface area reduction at 4 weeks was 38.5%; 11 out of 22 (50%) DFUs and 13 out of 28 (46.4%) VLUs had achieved ≥ 40% closure. The mean percent wound surface area of pressure ulcers (n = 3) was not calculated due to a low significant number of cases, and the small population was not specific enough to relate to clinical data. Mean percent wound surface area reduction was 73.3% at week 8 and 91.3% at week 12.

At 12 weeks, 31 out of 53 (58.5%) wounds were fully reepithelialized, and an additional 12 out of 53 (22.6%) of the remaining wounds were at least 80% closed. Mean percent wound surface area reduction by wound type at week 12 is shown in Figure 1. All wounds were 100% reepithelialized by week 20 except 1 DFU that reepithelialized at week 24. Average time to closure for all wounds was 10.6 weeks (range, 5–24 weeks). Outcomes by

Table 2. Patient outcomes

	n (%)	Avg area at wk 0 (cm^2)	Avg time to closure (wk)	Avg % area closed at wk 4	Avg % area closed at wk 8	Avg % area closed at wk 12	≥40% closed at wk 4 n (%)	≥40% closed at wk 8 n (%)	80%–99% closed at wk 12 n (%)	100% closed at wk 12 n (%)	100% closed at wk 20 n (%)
All wounds	53 (100)	5.8	10.6	38.5%	73.3%	91.3%	25 (47.2)	49 (92.5)	14 (26.4)	31 (58.5)	52 (98.1)
DFU	22 (41.5)	6.4	10.6	38.1%	76.5%	90.6%	11 (50.0)	20 (90.9)	9 (40.9)	13 (59.1)	21 (95.5)
VLU	28 (52.8)	5.8	10.4	39.2%	70.9%	92.6%	13 (46.4)	26 (92.9)	4 (14.3)	17 (60.7)	28 (100)
PrU	3 (5.7)	2.3	12.0	35.1%	72.0%	84.3%	1 (33.3)	3 (100)	1 (33.3)	1 (33.3)	3 (100)

Avg: average; DFU: diabetic foot ulcer; VLU: venous leg ulcer; PrU: pressure ulcer

wound type are listed in Table 2. All patients responded well to treatment, with no reported adverse reactions or adverse side effects. Average weekly cost of care for the first 4 weeks was approximately $276.50 based on 2 visits per week, and the average cost of care for 1 wound episode (from presentation to closure, average time to closure: 10.6 weeks) was $2749.49.

The following 2 presented patients represent various etiologies with clinical outcomes that match the conclusion and results of this retrospective cohort study with accuracy and can be demonstrated as typical wounds that were treated in this particular author's clinic.

Case 1: ankle wound with exposed tendon. A 66-year-old man with diabetes presented with a left ankle wound with exposed anterior tibialis tendon (Figure 2A), secondary to excessively high pressure underneath a gauze wrap that was used to help treat the patient's heel pressure ulcer. Prior to presentation at the clinic, the patient was self-treating the wound when he changed the dressing and over-tightened the gauze wrap. Patient had history of type 2 diabetes mellitus and human immunodeficiency virus. His glycated hemoglobin (HbA1c) was 7.6% and BMI was 28.78.

Five minutes after applying a sodium hypochlorite cleanser application, the wound bed was surgically debrided. A CECM dressing was applied and covered with a GV/MB antibacterial PU foam dressing and a secondary gauze dressing. Dressings were changed twice weekly for the first 4 weeks and once weekly thereafter (Figure 2B-2D) until the wound closed at 15 weeks (Figure 2E).

Case 2: VLU in an obese patient with diabetes. A 93-year-old woman presented with a left lower leg venous insufficiency ulcer secondary to type 2 diabetes mellitus and severe obesity (Figure 3A). The ulcer had been present for 6 weeks prior to initial visit, during which time it was treated with hydrogen peroxide cleanser with antibiotic ointment and dry gauze changed daily. Her HbA1c measured 6.5% and BMI was 38.01.

Her wound was surgically debrided, and a CECM dressing was applied with a GV/MB antibacterial PU foam dressing cover, a secondary gauze dressing, and compression. The wound was debrided weekly, and dressings were changed twice weekly for the first 4 weeks (Figure 3B, 3C). After 4 weeks, dressings were changed once weekly (Figure 3D) until ulcer closed at week 8 (Figure 3E).

Discussion

Overall, debridement and the use of CECM dressings with GV/MB antibacterial PU foam dressings in an advanced age population with above normal BMI was successful with an average time to closure of 10.6 weeks for the wounds treated in this series. It is interesting to note that 27 out of 28 (96.4%) wounds that did not achieve > 40% wound surface area reduction by week 4 progressed to complete closure by week 20, with no additional wound treatment besides debridement and the CECM and GV/MB antibacterial PU foam dressing regimen. Further analysis found that patients with < 40% wound area reduction by week 4 had smaller wounds at presentation (4.8 cm^2 vs. 7.0 cm^2), were older (77.4 years vs. 74.2 years), had a higher BMI (29.5 vs. 26.9), and averaged slower time to closure (12.7 weeks vs. 8.2 weeks), compared with patients who achieved ≥ 40% wound area reduction by week 4. Of those 25 wounds that achieved ≥ 40% wound area reduction by 4 weeks, 21 (84%) were closed at week 12, compared with only 10 out of 28 (35.7%) wounds with ≤ 40% wound area reduction by week 4.

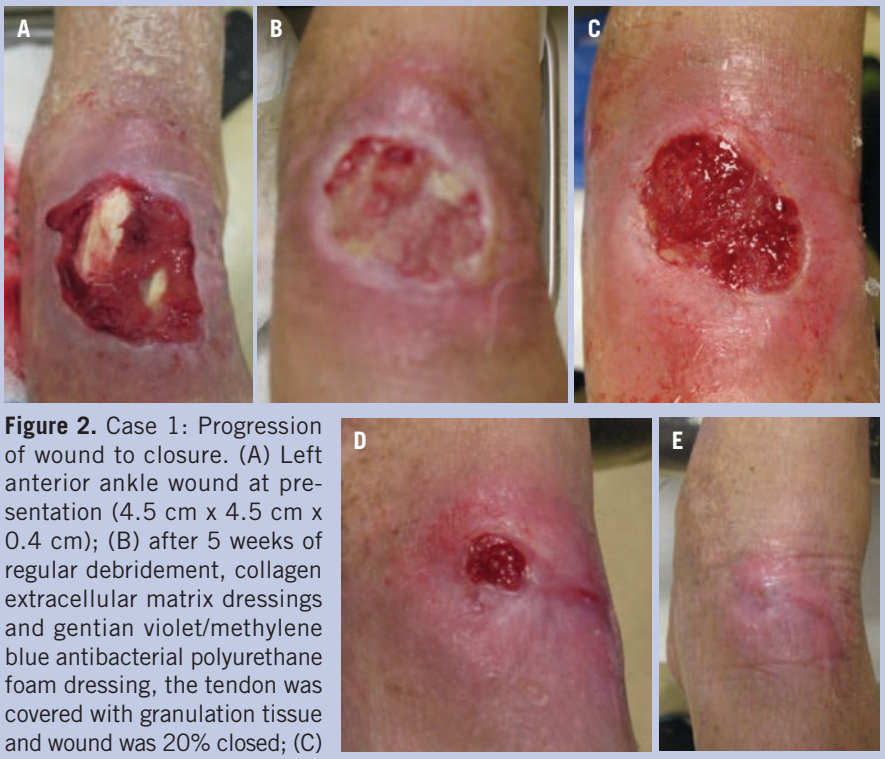

Figure 2. Case 1: Progression of wound to closure. (A) Left anterior ankle wound at presentation (4.5 cm x 4.5 cm x 0.4 cm); (B) after 5 weeks of regular debridement, collagen extracellular matrix dressings and gentian violet/methylene blue antibacterial polyurethane foam dressing, the tendon was covered with granulation tissue and wound was 20% closed; (C) at week 7, wound was 100% granulated with contraction of wound edges; (D) at week 13, wound was 93% reepithelialized; and (E) the ankle wound was healed at week 15.

Compared with VLUs, DFUs showed a slightly greater percent wound surface area reduction rate at week 8, but a lesser area reduction at week 12. This is consistent with the author's observation that DFUs in this series took longer than VLUs to progress to full closure during the reepithelialization phase, but considerably more research is required to validate this observation. No conclusions could be made regarding pressure ulcer healing in this series due to low subject numbers. Additionally, all wounds in this series were open for at least 4 weeks prior to initial presentation at the treating clinic. Since the author did not have access to the patients' wound healing progression data prior to initiating CECM dressings, the change in healing trajectory with use of CECM dressings is unknown.

During the first 4 weeks of treatment, patients were seen twice weekly to more aggressively address inflammation and healing of the chronic lower extremity wounds and to verify dressing integrity. The aim was to quickly reduce elevated protease activity, especially MMP-9 (gelatinase B) prominence in the wound, as high levels of active MMP-9 have been implicated as an important contributor to delayed healing.[17,18] In addition to dressing placement, the first weekly visit of the initial 4 weeks of treatment was focused on debridement and exudate management, and the midweek visit objective was to ensure periwound skin integrity, a healthy wound bed, and efficient management of exudate as well as verifying integrity of the dressing. More frequent visits to wound care clinics have been shown to enhance compliance, decrease time to closure, lower hospital readmission rates, and lead to reduced health care expenditures for certain patients with DFUs and VLUs.[19]

The recommended CECM dressing application frequency is every 5 to 7 days or as needed. During at least the first 4 weeks of treating the chronic wounds, the author found there was no visible presence of the CECM dressing after 3 to 4 days in the wound, and a new CECM dressing needed to be applied. When inflammation decreased and the wound was stable and progressing toward closure (usually by week 5), CECM dressings remained visible in the wounds for longer periods of up to 7 days.[20] Based on this experience, and for the purpose of consistency, the author switched the clinic visit frequency to once weekly after the initial 4 weeks. In the author's experience, a new CECM dressing should be placed about the time there is no visible presence on the wound bed of the previously placed CECM dressing. In all 53 patients in this series, there was no visible presence of CECM dressings upon removal of the cover dressing at any of the dressing changes, so in all cases, a new CECM dressing was placed at each dressing change.

Fife and Carter[21] reported a mean cost to closure per wound in the US Wound Registry (5240 patients with 7099 wounds) of $3927. Average wound surface area was 19.5 cm^2, average patient age was 61.7 years, and mean number of serious comorbid conditions (mostly diabetes and obesity) was 1.8.[21] Outcomes extracted from the Registry can be ideal "real world" comparators since the registry contains data of patients with multiple comorbidities treated in a variety of outpatient care settings, which reflects real-life practice.[21] Elements of cost in the Registry included the billed advanced practitioner fee for one visit,

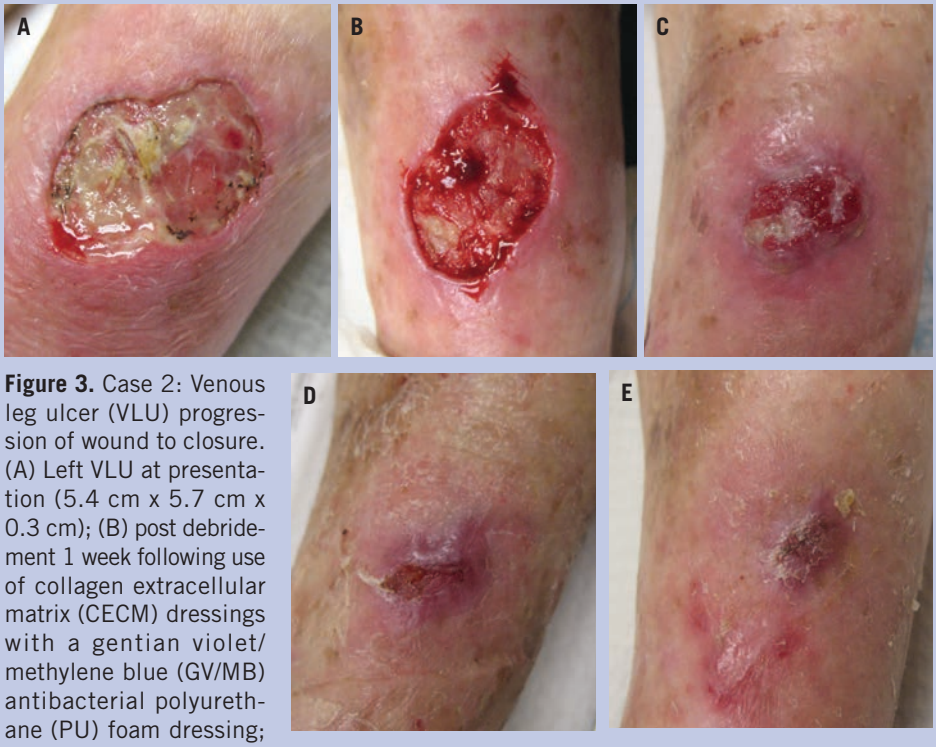

Figure 3. Case 2: Venous leg ulcer (VLU) progression of wound to closure. (A) Left VLU at presentation (5.4 cm x 5.7 cm x 0.3 cm); (B) post debridement 1 week following use of collagen extracellular matrix (CECM) dressings with a gentian violet/methylene blue (GV/MB) antibacterial polyurethane (PU) foam dressing; (C) wound was 77% reepithelialized after 4 weeks of CECM dressings with GV/MB antibacterial PU foam dressing; (D) at week 6, wound was 96% closed; and (E) ulcer was fully reepithelialized at week 8.

the billed facility fee for that day's visit, billed procedure costs for that day (eg, bioengineered skin application, debridement, compression bandaging), and the estimated cost of all wound care dressings and therapies over the whole course of treatment.

In the present series, the average per patient cost of episode of care was approximately $2749; this is 30% less than the average per patient cost of wound care reported in the Registry[21] (Table 3). Cost calculations for this analysis did not include compression bandaging or gauze, but otherwise included similar elements as the Registry. Compared to Registry data, the average wound surface area at presentation in the current series was smaller and average patient age was higher; these variables were not controlled for in the present analysis. In addition, patient care in this series took place at a single, freestanding wound clinic office of a qualified health care professional. Even allowing for these differences, it appears the cost of care to treat wounds in the present series was well under the real-world average, despite the effects of advanced age and multiple serious comorbidities on the patient population. It is conceivable that the smaller wound sizes in the patient population presented study herein could have contributed to a lesser overall cost compared with Fife and Carter[21]; however, without direct treatment-to-dressing comparative data, these numbers can only be anecdotally reviewed and compared. Larger controlled cost studies are needed to quantify actual cost savings.

The CECM dressings are prepared from propria submucosa of ovine forestomach tissue sourced from New Zealand using processes to delaminate and decellularize the tissue.[15,16] It has been proposed that the effectiveness of a CECM dressing is predicated in its structure as an intact collagen matrix dressing.[11,22] Mechanisms of action of an intact collagen dressing include binding growth factors, regulating cell activity, facilitating intercellular communication, serving as a scaffold to hold cells together, and providing structural support to help tissue repair in both acute and chronic wounds.[8]

Instructions for the use of a CECM dressing call for securing the dressing with an appropriate cover such as a border foam dressing or any standard foam dressing. The cover dressing can be any secondary dressing that manages exudate appropriately. Any foam dressing can be placed for absorption. The author chose to use a foam dressing with broad spectrum antibacterial properties to help address bacterial bioburden, but the foam cover dressing does not need antibacterial properties for the function of the CECM dressing. The purpose of the GV/MB foam dressing was to facilitate wicking of wound exudate into the foam dressing and protect the wound from the external environment. The 2 organic pigments (methylene blue and gentian violet) bonded to the foam to create a microenvironment meant to inhibit the growth of microorganisms.[23] The antibacterial and absorptive characteristics of the foam may have contributed an incremental effect on wound healing (but was not measured); any added or symbiotic effect, whether

Table 3. Mean cost to closure per wound in US Wound Registry versus the current study

	Patients (N)	Wounds (N)	Average wound surface area (cm^2) at admission	Average patient age	Mean serious comorbid conditions (n)	Mean cost to closure per wound
US Wound Registry[21]	5240	7099	19.5	61.7	1.8	$3927
Current study	53	53	5.8	75.9	Data not extracted	$2749

beneficial or detrimental, of the cover dressing in this series is unknown. The author has observed similar effects on wounds with use of other foam cover dressings in combination with CECM dressings. A comparative study of wound healing outcomes with CECM dressings and various secondary cover dressings would be useful to guide product selection.

To the best of the author's knowledge, this is the largest retrospective cohort study to date that documents the incremental rate of closure over time of chronic wounds treated with CECM dressings and GV/MB antimicrobial PU dressings. A previously published retrospective case series analysis[13] of 23 VLUs treated with CECM dressings and regular debridement reported that all 23 ulcers (100%) healed during an average of 7.3 weeks (range, 2–15 weeks). Mean percent wound surface area reduction of all wounds was 97.9% at week 12, and 50% of wounds treated with CECM were closed by 7 to 8 weeks.[13] In the present study, only 4 out of 28 (14.3%) VLUs were 100% closed at week 8. This difference could be caused by a variety of factors including the advanced age of the patients included herein compared with the patient population in Bohn and Gas[13] (75.9 vs. 55.3 years).

The present results are similar to those of Liden and May[12] in their evaluation of CECM dressings for the treatment of recalcitrant wounds, which included venous, diabetic, and incisional wounds, in 19 patients with 24 wounds. At 12 weeks, 50% of wounds had closed, and the mean percent wound surface area reduction was 73.4%.[12] However, an accurate comparison of the present results with existing wound studies is difficult because of differences in study designs and samples.

The CECM dressings in the present study were placed only after appropriate debridement. The type of gauze wrap applied over the GV/MB antibacterial PU foam dressings was determined based on the level of exudate in the wound. An important cost aspect of ovine-based CECM dressings is that they are classified for reimbursement as a collagen dressing versus an advanced wound care matrix dressing, and therefore can be applied from the initial visit rather than waiting the requisite 3 to 8 weeks of moist wound healing dressing application typically required by the Centers for Medicare and Medicaid Services and private payers prior to initiating an advanced wound care matrix dressing.[24,25] The dressings have a 36-month shelf life and can be applied by patients, physicians, nurses, or any other caregiver in any care setting.

Results of this analysis showed the healing of chronic wounds in this series could be achieved with regular debridement and a relatively inexpensive collagen matrix and antibacterial dressing regimen (compared to the respective overall cost of care in Fife and Carter[21]), even in patients of advanced age, with an above average BMI, and in wounds that did not achieve > 40% wound surface area reduction by week 4. The data are promising but have all the limitations of an uncontrolled, retrospective case series analysis including lack of a comparator, patient selection bias, differences in wound care techniques between clinicians, and potential flaws in recordkeeping. The relatively small patient sample size and single-center site bias are additional limitations. A larger, controlled study of wound closure outcomes with both individual and combination use of CECM dressings and GV/MB antimicrobial PU dressings is needed to understand the incremental effect of each of the dressings on healing.

Conclusion

Healing of chronic wounds in this series was achieved with regular debridement and a relatively inexpensive collagen matrix and antibacterial dressing regimen, even in patients of advanced age, with an above average BMI, and in wounds that did not achieve > 40% wound surface area reduction by week 4. The average cost of care for a single wound episode in this series was $2749, which was under the real-world mean cost to closure per wound of $3927 reported by Fife and Carter based on US Wound Registry data.[21] Although this is the largest case series to date evaluating chronic wound closure with CECM dressings and GV/MB antimicrobial PU dressings, larger, controlled research is needed to determine the comparative cost and clinical effectiveness of this dressing combination in treating chronic lower extremity wounds.

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Use of an Ovine Collagen Dressing with Intact Extracellular Matrix to Improve Wound Closure Times and Reduce Expenditures in a US Military Veteran Hospital Outpatient Wound Center

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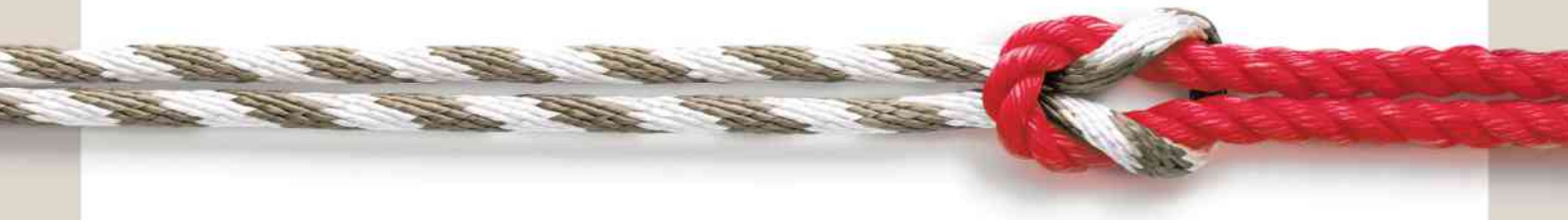

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Use of an Ovine Collagen Dressing with Intact Extracellular Matrix to Improve Wound Closure Times and Reduce Expenditures in a US Military Veteran Hospital Outpatient Wound Center

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ABSTRACT

A novel, comprehensive decision-making and treatment algorithm was established within a US government-run military veteran hospital in an attempt to standardize the process of outpatient wound care and streamline costs. All patients were systematically evaluated and treated using the comprehensive algorithm over a span of nine months. After three months of adherence to the algorithm, the algorithm was modified to include ovine-based collagen extracellular matrix (CECM) dressings as a first-line conventional treatment strategy for all appropriate wounds. The purpose of this retrospective analysis was to evaluate the hospital's change in cellular and/or tissue-based graft usage and cost, as well as wound healing outcomes following modification of the wound care standardization algorithm. Data from the first quarter (Q1; three months) of protocol implementation were compared to the subsequent two quarters (six months), during which time the first-line dressing modification of the protocol was implemented. Results showed that between quarters 1 and 3, the percentage of wounds healed increased by 95.5% (24/64 to 80/109), and the average time to heal each wound decreased by 22.6% (78.8 days to 61.0 days). Cellular and/or tissue-based

graft unit usage decreased by 59.7% (144 units to 58 units), and expenditures on cellular and/or tissue-based grafts decreased by 66.0% ($212,893 to $72,412). Results of this analysis displayed a trend toward decreased expenditures, faster healing times, and a greater number of healed wounds following modification of an evidence-based algorithm to incorporate CECM dressings as a first-line treatment strategy in managing chronic wounds.

INTRODUCTION

Chronic ulcers affect more than 6.5 million people in the US and are a major growing health problem due to an aging population, increasing health care costs, and a steep rise in diabetes and obesity worldwide.[1] The prevalence of venous insufficiency ulcers in the US is approximately 600,000 annually,[2] and venous leg ulcers (VLU) account for at least 70% of all chronic ulcers found on the lower leg.[2,3] In 2014, approximately 22 million people in the US were living with diagnosed diabetes,[4] and, of these diabetics, an estimated 10–15% will develop a foot ulcer during their lifetime.[5] These foot ulcers represent a substantial cost burden, estimated at a one-year cost of over $9 billion among US Medicare beneficiaries with diabetes.[6] In 2013, the average cost of treating a diabetic foot ulcer (DFU) patient was approximately $49,209 for the two-year period after diagnosis.[5] Compared to matched non-VLU patients, a large database analysis showed VLU patients incurred annual incremental medical costs of $6,391 in Medicare costs and $7,030 in private insurance costs, suggesting an annual US payer burden of $14.9 billion for VLUs.[7]

A focus on reductions in acute care spending has transferred care to the outpatient setting, and a growing number of hospitals are offering outpatient wound services as part of this cost shifting. Currently, there are more than 1,000 outpatient wound care centers in the United States[8] with alarming estimated annual expenditures on wound care services of over $50 billion.[9] These expenditures have captured the attention of US Centers for Medicare and Medicaid Services (CMS) administrators who have been moving to gain control of the overwhelming costs of outpatient wound services. CMS introduced several sweeping cost saving measures in 2014, and there is a major shift underway toward value-based payments, versus the present fee-for-service payments.[10,11]

Along similar lines of quality improvement and cost savings, within the US Veterans Affairs (VA) hospital system, there has been a major push toward standardization since the August 2001 launch of a Healthcare Failure Mode and Effect Analysis (HFMEA) process.[12] HFMEA is a five-step process that uses an interdisciplinary team to proactively evaluate a health care process. It involves process flow diagramming, a hazard scoring matrix, and a decision tree to identify and assess potential vulnerabilities. This standardization process was originally designed to assess and address prospective risk of a health care process to enhance safety, but the process is now also used to streamline cost.

Basic tenets of HFMEA were used to standardize the process of wound care within a US VA hospital in an attempt to improve outcomes and reduce cost. Prior to standardizing the wound care process in this VA hospital, inpatient and outpatient wound care was performed on all floors and in all departments by numerous physicians and clinicians with varying levels of wound care training. A substantial proportion of hospital expenditures were spent on wound care, outcomes were not tracked, and patients were regularly lost to follow-up. Diabetic foot and venous leg ulcers were reported causes of extended lengths of stay and increased emergency department admissions. Following committee analysis of the problem, a wound healing center was established within the hospital and a two-part wound care standardization algorithm was developed and implemented.

Goals of the wound healing center and the algorithm were to standardize wound care efforts and product usage throughout the facility, to increase the rate of wound resolution, and to decrease overall expenditures on wound care. After three months of adherence to the algorithm, the algorithm was modified to include an ovine-based collagen extracellular matrix dressing (CECM; Endoform® dermal template, Hollister Incorporated, Libertyville, Illinois) as a first-line treatment strategy for all appropriate wounds based on its understood effects in reducing elevated metalloproteinases (MMPs)[13] and its relatively low cost. The purpose of this retrospective analysis was to evaluate the hospital's change in cellular and/or tissue-based graft usage and cost, as well as wound healing outcomes following modification of a wound care standardization algorithm to include CECM dressings as a first-line treatment strategy.

MATERIALS AND METHODS

A 1,150 ft^2 outpatient wound healing center was established within the VA hospital, and all ancillary departments were educated about the wound healing center services and how to refer patients to the center. A dual algorithm that combined decision-making and wound treatment protocols was developed and implemented by the wound healing center program director (Daniel T. Ferreras) (Fig. 1). Wound healing staff members were educated about the systematic use of the algorithm for each patient.

Decision protocol

Part one of the algorithm (Decision Protocol) is a decision tree honoring the fundamentals of wound care and was used to determine that both the patient and wound bed were ready for treatment. The Decision Protocol was based

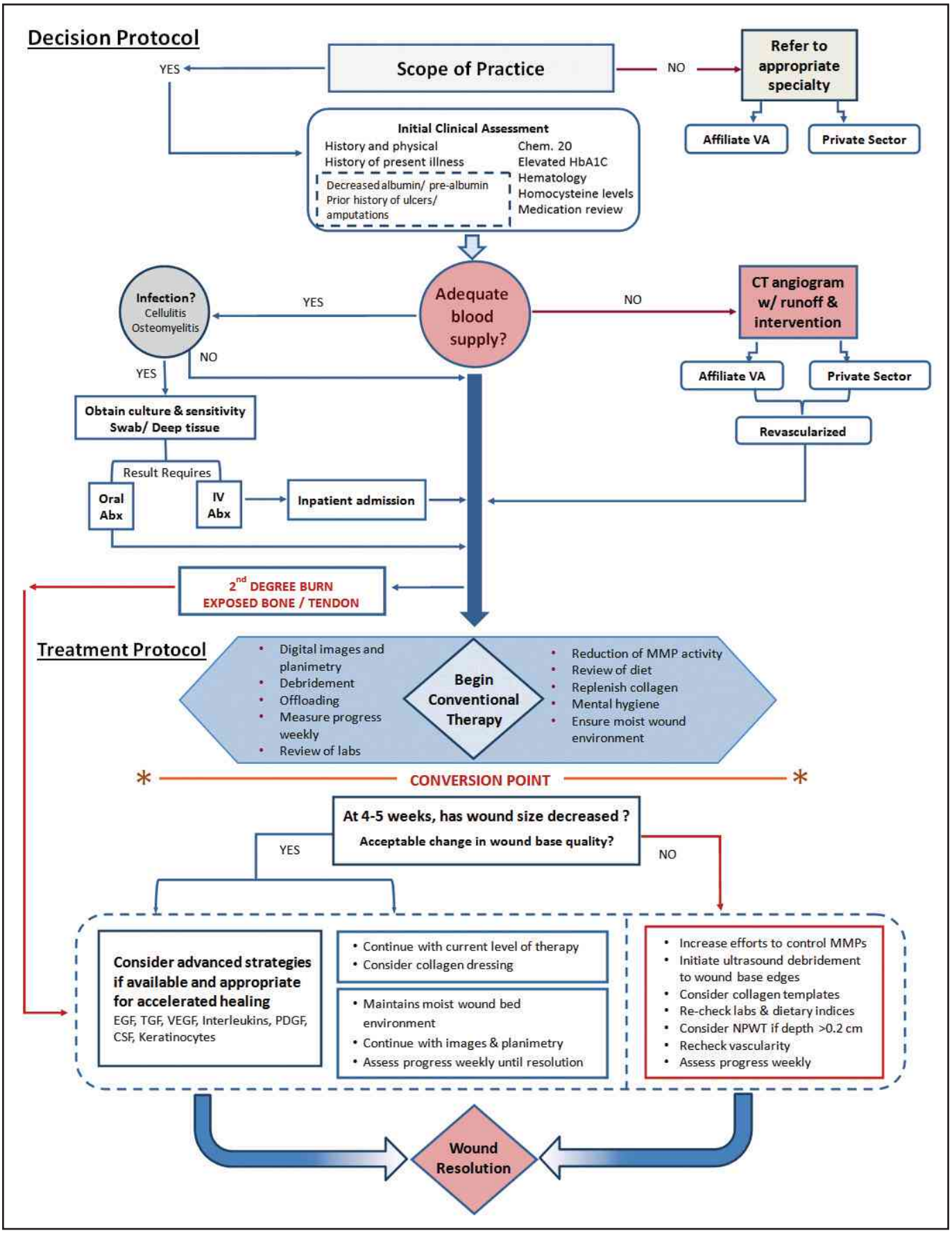

Figure 1. Dual protocol algorithm.

Table I
Patient demographics and outcomes

	Q1 Sept-Nov. 2014	Q2 Dec. 2014-Feb. 2015	Q3 Mar-May 2015
Patients (n)	79	78	73
Male, n (%)	76 (96.2)	76 (97.4)	71 (97.2)
Female, n (%)	3 (3.8)	2 (2.6)	2 (2.7)
Average age (years)	66.5	64.5	65.4
Wounds treated (n)	64	84	109
DFU, n (%)	35 (54.7)	65 (77.4)	82 (75.2)
VLU, n (%)	25 (39.1)	17 (20.2)	21 (19.3)
Heel PrU, n (%)	4 (6.2)	2 (2.4)	6 (5.5)
Clinic visits (n)	274	343	336
Healed wounds (n;%)	24 (37.5)	55 (65.5)	80 (73.3)
DFU, n (%)	18 (51.4)	44 (67.7)	61 (74.3)
VLU, n (%)	3 (12.0)	9 (52.9)	16 (76.2)
Heel PrU, n (%)	3 (75.0)	2 (100.0)	3 (50.0)
Average time to heal, days (weeks)	78.8 (11.3)	77.2 (11.0)	61.0 (8.7)
DFU, n (%) (weeks)	74.2 (10.6)	67.9 (9.7)	52.5 (7.5)
VLU, n (%) (weeks)	86.1 (12.3)	115 (16.5)	99 (14.2)
Heel PrU, n (%) (weeks)	73.5 (10.5)	57.4 (8.2)	44.1 (6.3)

Table II
Dressing usage and expenditures

	Q1 Sept-Nov. 2014	Q2 Dec. 2014-Feb. 2015	Q3 Mar-May 2015
Cellular and/or tissue-based graft units used (n)	144	84	58
CECM units used (n)	0	50	40
Total cost of cellular and/or tissue-based grafts ($US)	212,893	115,096	72,412
Avg. cellular and/or tissue-based graft cost/treated ulcer ($US)	3,326	1,370	664
Total cost of CECM units ($US)	0	1,363	1,253

on five fundamental factors necessary for wound healing: optimized perfusion (compression when needed), offloading properly, control of infection/bioburden, debridement of devitalized tissue, and balanced nutrition according to the specific needs of the patient.[14-18] Each of these fundamentals was addressed by the wound healing team through systematic use of the decision protocol. Once the fundamentals were addressed, and if the patient did not have a first or second degree burn or exposed tendon,[19] the patient could proceed to the treatment protocol.

Treatment protocol

Part two of the algorithm (Treatment Protocol) was used to guide treatment for each patient once the wound and patient were prepared. For the first three months after algorithm implementation, oxidized regenerated cellulose (ORC)/collagen dressings were used as first-line conventional treatment for all appropriate chronic wounds. Based on the needs of our chronic wound population and growing evidence implicating MMP imbalances as a critical factor in stalled wounds,[20] a decision was made to switch to CECM dressings as a first-line conventional treatment strategy after three months (beginning of quarter 2). Silicone fenestrated gauze or an antibacterial foam dressing bound with gentian violet and methylene blue (GV/MB) (Hydrofera Blue®; Hollister Incorporated, Libertyville, Illinois) was used as a cover over the CECM dressing, and paper tape was used to secure the cover dressing. The area was wrapped with a latex-free conforming stretch bandage and a light four inch self-adherent elastic wrap as needed.

Compression stockings and appropriate off-loading strategies (controlled ankle movement walker boot, offloading padding, and total contact cast) were used as needed. At weekly follow-up appointments, diet was reviewed, and wounds were debrided and irrigated as necessary. Changes in granulation tissue and wound dimensions were recorded, and wounds were photographed using a 16 megapixel digital camera system.[21] Wounds were reassessed at four, eight, and 12 weeks for progress.

If the wound size continued to contract after four to five weeks of conventional treatment, CECM dressings remained the primary dressing. If wound contraction stalled or wound size increased after four to five weeks, a cellular and/or tissue-based graft was chosen in lieu of CECM dressings to reach our resolution endpoint. The selection of cellular and/or tissue-based products was varied and included cryopreserved placental membrane, dehydrated human amnion/chorion membrane allograft, human fibroblast-derived skin substitute, living bi-layered skin substitute, and fetal bovine dermal scaffold materials.

Acceptable change in wound-base quality was defined as beefy red granulation tissue, limited or no hypergranulation, and no wound edge epibole. The wound was considered resolved when there was 100% re-epithelialization and no drainage.

Data analysis

Demographic, dressing usage, and outcomes data from September 15, 2014 to May 31, 2015 were retrospectively extracted from the electronic medical records, and entered into an Excel® (Microsoft Inc., Redmond, Washington) spreadsheet to calculate totals and averages. Endpoints measured were number of healed wounds, time to heal, and cost and units used of cellular and/or tissue-based grafts and CECM dressings. Data from the first quarter (three months) of protocol implementation were compared to the subsequent two quarters (six months) during which time the first-line dressing modification of the protocol was implemented.

RESULTS

Patient demographics and outcomes are listed by quarter in Table I. The total number of patients treated and average age were similar during all three quarters. The number of wounds treated increased by 70.3% (64 in Q1 to 109 wounds in Q3) and the number of clinic visits increased by 22.6% (274 in Q1 to 336 visits in Q3) between quarter one and three. During this same timeframe, the percentage of wounds healed increased by 95.5% (24/64 [37.5%] in Q1 to 80/109 [73.3%] in Q3), and the average time to heal each wound decreased by 22.6% (78.8 days in Q1 and 61.0 days in Q3).

Between quarters 1 and 3, cellular and/or tissue-based graft unit usage decreased by 59.7% (144 units in Q1 and 58 units in Q3), and expenditures on cellular and/or tissue-based grafts decreased by 66.0% ($212,893 in Q1 and $72,412 in Q3) (Table II, Figs. 2 and 3).

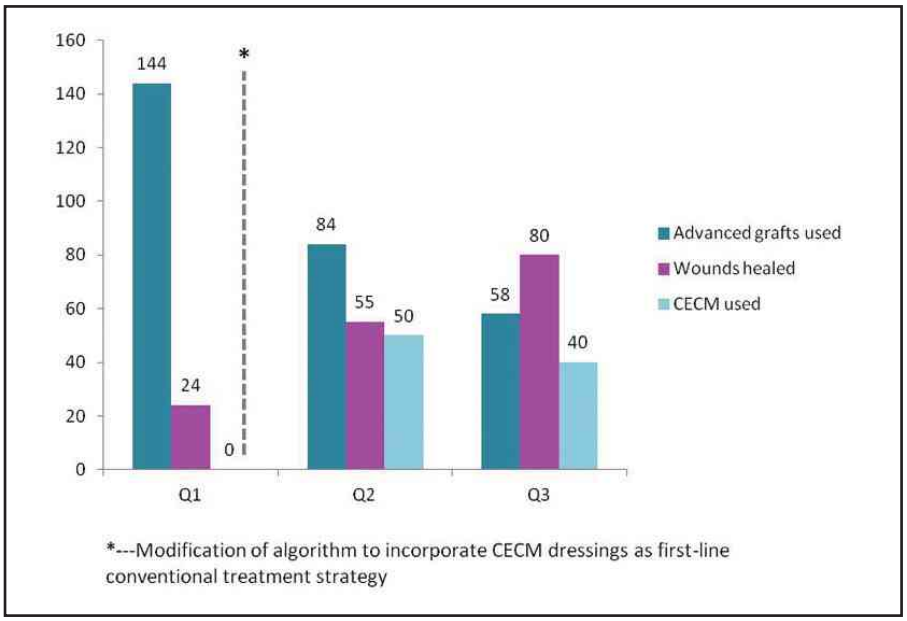

Figure 2. Cellular and/or tissue-based graft/CECM unit usage and wounds healed over time.

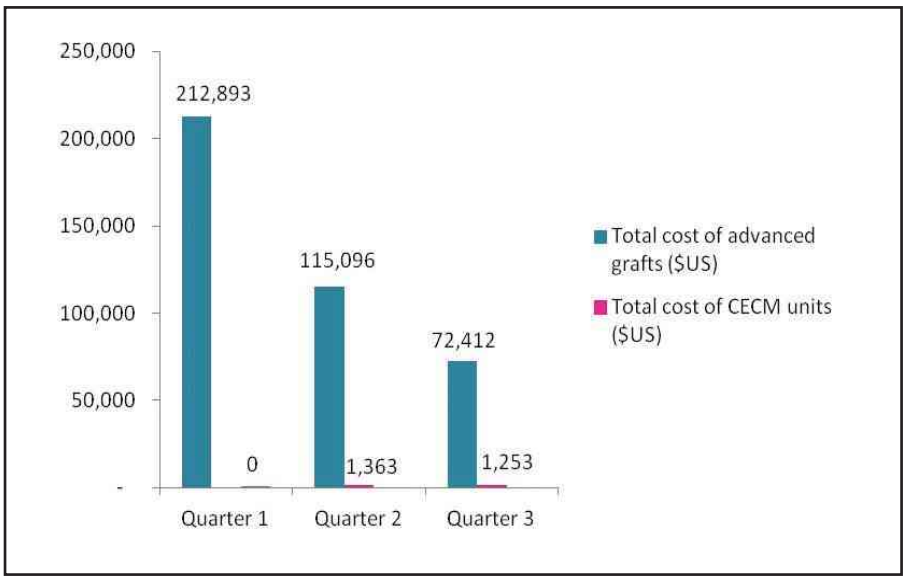

Figure 3. Cellular and/or tissue-based graft and CECM unit expenditures over time.

CASE STUDIES

Case Study 1: Diabetic foot ulcers in a patient with peripheral vascular disease

A 60-year-old male presented with diabetic foot ulcers on the hallux and second digit of his left foot (Figs. 4a and 4b). The man had type 2 diabetes with a medical history of neuropathy, syncopal events, sleep apnea, obesity, anemia, depression, peripheral vascular disease (PVD), coronary arteriosclerosis, acute osteomyelitis of the lower extremity (left), monoclonal paraproteinemia, and retinal detachment (legally blind). The wounds were ultrasonically debrided at initial presentation to remove eschar. Patient and wound preparation included attention to daily diet, noninvasive vascular diagnostic testing (arterial duplex ultrasound, CT-angiography), vascular intervention with stents, and mental/spiritual counseling.

After wound bed preparation, a CECM dressing was applied with a GV/MB foam dressing as a cover dressing. The foot was offloaded with a post-operative surgical shoe, and wounds were surgically debrided at each weekly dressing change. At week nine, a bi-layered skin substitute was applied to the wound (Fig. 4c) in an attempt to speed resolution. CECM dressings were continued after the bi-layered skin substitute, and a fetal bovine dermal repair scaffold (rich in type III collagen) was placed on week 12 to help speed restoration of the collagen-rich wound bed after the patient sustained a deep injury to the foot ulcers and set wound healing backward several weeks. CECM dressings were continued (Figs. 4d and 4e) until both ulcers were fully healed at 6 1/2 months (Fig. 4f).

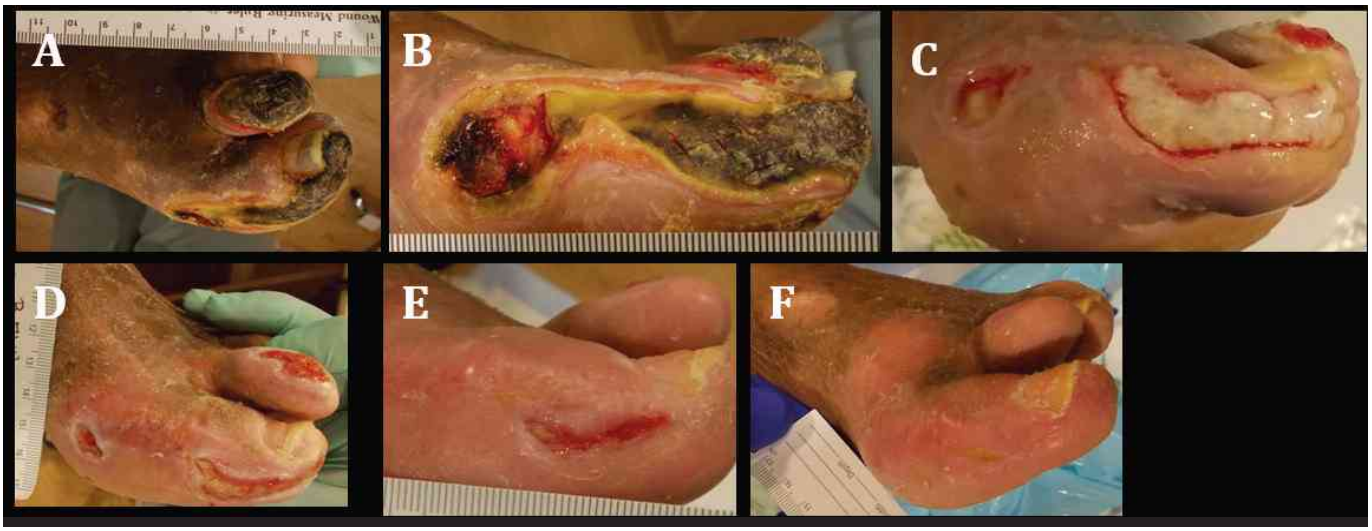

Figure 4. a) and b) At presentation, eschar-covered ulcers on the left hallux and second digit measured 9.5 x 2.0 cm and 4.5 x 3.5 cm, respectively. CECM dressings were initiated with a GV/MB foam cover dressing. c) Bi-layered skin substitute applied at nine weeks. CECM dressings were continued subsequently. d) DFUs after three months of CECM dressings and two skin substitute applications. e) Ulcers nearly re-epithelialized at five months. f) At 6 1/2 months, ulcers are completely healed.

Case Study 2: Bilateral diabetic foot ulcers in a patient on anticoagulant therapy

A 64-year-old diabetic male presented with three diabetic foot ulcers under the metatarsal heads on the plantar aspects of both feet (Figs. 5a and 5b). Wounds had been present for four to five weeks. The patient was diabetic with a history of neuropathy, multiple type hyperlipidemia, PVD, hypertension, nicotine dependence, non-compliance issues, vitamin B-12 deficiency, coagulation therapy (treated with warfarin), depressive disorder, iron deficiency, coronary artery disease, pes cavus feet, varicose veins, and sleeplessness.

Wounds were mechanically and ultrasonically debrided. CECM dressings (2 x 2 cm) were sized and placed in all ulcers and GV/MB dressings (2.5 x 2.5 cm) were used as cover dressings. Both feet were offloaded with wedge offloading shoes. CECM dressings were applied once per week with weekly progression measured at each dressing change (Figs. 5c–5g). At each monthly evaluation, all ulcers achieved adequate wound healing progression (40 to 50% smaller) to continue with CECM dressings for the duration of therapy. The right foot ulcer was fully healed at eight weeks and the left foot ulcers were healed at six weeks.

Case Study 3: Post-amputation wound dehiscence in a diabetic patient

A 78-year-old male presented with a dehisced incision (Fig. 6a) following left hallux amputation 10 weeks prior. The patient was type 2 diabetic with a history of chronic congestive heart failure, atrial fibrillation, obesity, chronic obstructive pulmonary disease, hyperlipidemia, anemia, PVD, hypothyroidism, hypertension, age-related macular degeneration, benign prostatic hyperplasia, and insomnia. The wound had been treated with negative pressure wound therapy (NPWT) for two weeks prior to presentation. The patient wore

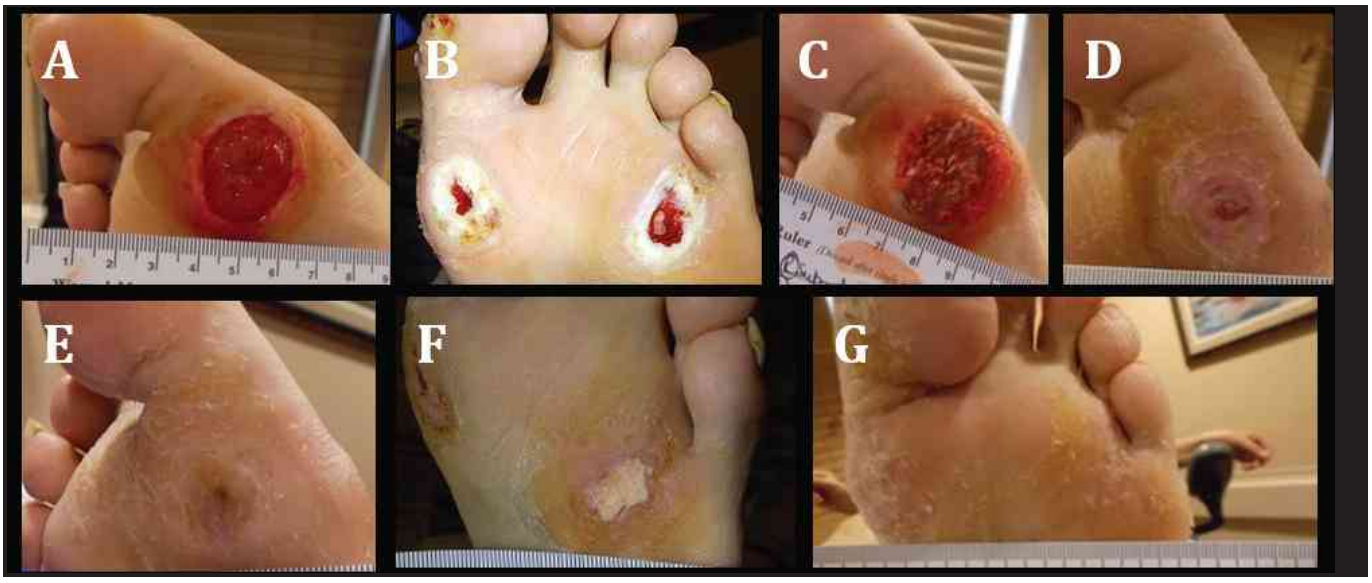

Figure 5. a) and b). Diabetic foot ulcers on right and left foot at presentation. c) Right foot ulcer edges are flattened after three weeks of CECM dressings. d) At seven weeks, right foot ulcer is nearly re-epithelialized. e) At eight weeks, right foot ulcer is healed. f) CECM dressing shown in left foot ulcer. g) Both left foot diabetic ulcers are 100% re-epithelialized after six weeks of CECM dressings.

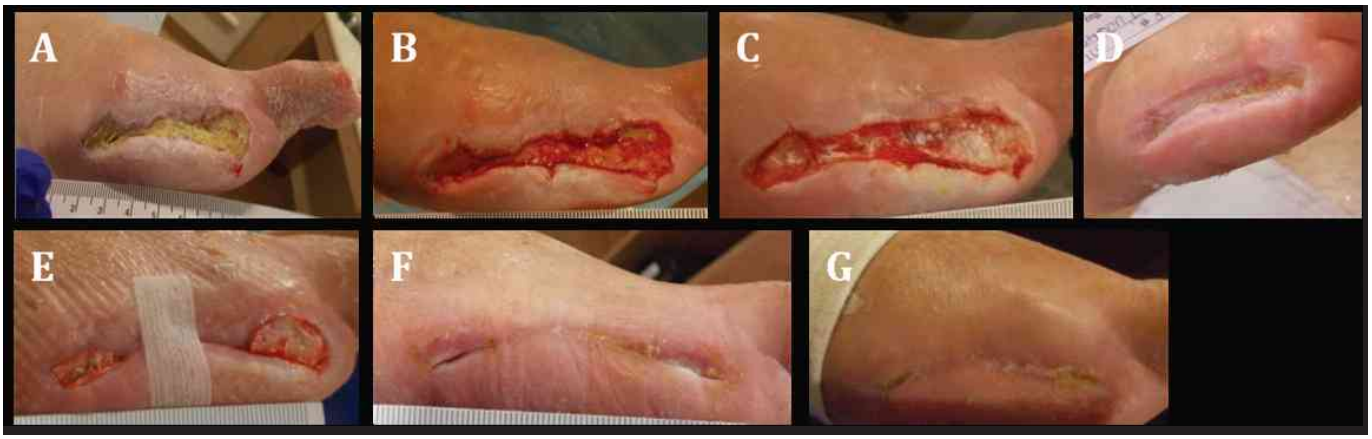

Figure 6. a) and b). Post-amputation wound at presentation and after debridement. c) After two weeks of combined CECM dressings and NPWT. d) After eight weeks of CECM dressings and NPWT and two applications of cryopreserved placental membrane grafts. e) At 12 weeks with CECM dressings. f) At 16 weeks with CECM dressings. g) Wound is fully re-epithelialized at 22 weeks.

a post-surgical shoe and ambulated in a wheelchair.

Excisional and ultrasonic debridement were performed, (Fig. 6b) and CECM dressings with a polyvinyl alcohol GV/MB foam dressing cover were initiated in tandem with NPWT, underneath the NPWT foam dressing. CECM dressings were applied once per week throughout treatment. Fig. 6c shows the wound after two weeks. Cryopreserved placental membrane grafts were placed with NPWT at weeks four and five. CECM dressings were continued and the wound volume was markedly decreased at weeks eight (Fig. 6d) and 12 (Fig. 6e). At week 16, a human amniotic membrane allograft was placed over the remaining wound areas, and CECM dressings were continued (Fig. 6f) until complete closure at 22 weeks (Fig. 6g).

DISCUSSION

This retrospective analysis displayed a clear trend toward decreased expenditures, faster healing times, and a greater number of healed wounds following implementation and modification of an algorithm to incorporate CECM dressings as first-line treatment of chronic wounds. While there were substantial increases from quarter to quarter in the number of wounds treated, as well as clinic visits and percent of wounds closed, expenditures on cellular and/or tissue-based grafts decreased by $140,481 between the first and third quarter.

Although the incremental effect of each of the implemented changes is unknown, these authors propose multiple factors that likely contributed to improved outcomes and lower costs. During the first quarter of operation, the number of patients was greater than the number of wounds treated because several patients who did not have a wound were consulted by primary-care physicians to be seen by the wound center for general podiatry services like partial nail avulsions. After the wound healing center sent out a special reminder delineating the scope of practice, services offered, and days/hours of operation, staff members began to better direct appropriate patients to the center.

Also, once a dedicated wound center staff was assembled and educated regarding the algorithm for decision-making and treatment, wound management became consistent and could be tracked. The two-part algorithm was developed to incorporate pivotal wound healing concepts that have been shown over the past 13 years to contribute positively to wound management from dermal defect to complete closure. Evidence-based modalities, such as offloading boots, were consistently incorporated into the management strategies and appeared to influence outcomes over time.

Establishing a target healing timeline may have improved results as well. For venous leg ulcers, a 20–40% reduction in wound area within two to four weeks has been found to be predictive of healing,[22] whereas for diabetic foot ulcers, a reduction of >50% by week four is predictive of healing.[23-25] We added one week to our algorithm, making it a four to five week timeframe before switching to a new dressing/therapy, to allow for real world uncontrollable factors like patient compliance, missed appointments, or other random events. Setting such quality measures will be a necessity for wound center survival in the future scenario of value-based reimbursement.

CECM dressing characteristics may also have contributed to the improved outcomes and lower costs observed in Q2 and Q3. The dressings are made from propria submucosa of ovine forestomach tissue using proprietary processes to delaminate and decellularize the tissue.[13,26] They consist of natural, intact collagen, including types I, III, and IV, as well as secondary ECM components such as elastin, fibronectin, laminin, and glycosaminoglycans.[27] The matrix dressing retains the three-dimensional architecture present in tissue ECM[27] and has demonstrated broad spectrum matrix MMP reduction.[13]

The new CECM/GV-MB dressing combination was less expensive per dressing than previously used dressings, but the primary reason for the switch was that we observed faster healing rates with the use of CECM dressings compared to our experience with C/ORC dressings. Our outcomes may also have been influenced by the antibacterial effects of the GV/MB foam cover dressings, but the incremental effect of the cover dressings is unknown. In our experience, CECM provided the strength of a dermal template but was simple to apply like a standard collagen-based dressing. CECM dressings could be applied as little as once per week and remained in the wound bed until they were no longer visible, which could save costs compared to other collagen dressings that

require applications up to three times per week.

These authors know of just two case series that have evaluated the use of CECM in chronic wounds. Bohn et al. (2014) reported, in a retrospective analysis, that 23 of 23 venous stasis ulcers healed in an average of 7.3 weeks (range: 2 to 15 weeks) with the use of CECM dressings.[28] This is considerably faster than the average time to heal VLUs in our study (14.2 weeks). In another series of 19 participants with 24 ulcers of various etiologies, the mean wound area decrease at 12 weeks with the use of CECM dressings was 73.4%.[31] Of the 24 wounds, eight (33%) were closed after eight weeks of treatment and 12 (50%) were closed at 12 weeks. Of wounds that closed, mean time to complete closure was 6.8 weeks, which is similar to our closure rate for DFUs and faster than our closure rate for VLUs.[29] Reasons for longer and inconsistent times to closure for VLUs in our study could be due to the comparatively advanced age of our patient population, as well as a historic lack of a specific process to identify VLUs within the VA system and the tendency for patients with VLUs to be referred to a VA wound clinic late in the disease course.[30]

This analysis contains all the inherent limitations of a retrospective, uncontrolled, nonrandomized study. Data were extracted from the first nine months of operation, which was a somewhat erratic period as the wound center was becoming fully functional. Small "settling in" adjustments were made throughout the study period that were undocumented and could have influenced outcomes. CECM dressings were introduced into the algorithm in Q2, and it is not possible from the data to know if there was a carryover effect from other treatment strategies. Cover dressing use and cost were also not considered in the analysis. Additionally, "wound closure" was tracked over time in quarterly increments, and the patients treated during each quarter were not mutually exclusive; therefore, the number of wounds treated in Q1 that were resolved in Q2 or Q3 was not determined. Clinician bias also may have skewed data results with respect to selection for, or timing of, a cellular and/or tissue-based graft. Long-term controlled studies are needed to determine the actual incremental effect on clinical outcome and cost of each of the variables within the systematic algorithm.

CONCLUSION

This publication describes the first attempt at implementing an evidence-based wound management algorithm within our VA hospital, or any VA facility within our Veterans Integrated Service Network. Algorithm modifications incorporating an MMP-modulating CECM dressing showed improved clinical outcomes and reduced advanced graft expenditures in this VA population. Our aim in developing a comprehensive algorithm is that it could serve as a roadmap for other wound care center directors in and outside of the VA system who are looking to decrease the use of more expensive modalities while improving quality of care.

Healing wounds more efficiently on the front-end—through the use of progressive algorithms—to reduce overall costs on the back-end fits with the current health care emphasis on evidence-based, outcome driven health care delivery systems. This pilot study/algorithm is novel in the VA system because, compared to non-VA hospital-based outpatient wound care departments in the US, there remains great access to advanced wound dressings and therapies, and administrators have not yet been forced to think of cost containment at every level. The benefits of this approach are broad reaching and include saving US taxpayer dollars and enhancing military veteran quality of care. STI

AUTHORS' DISCLOSURES

Daniel Ferreras is a consultant for Hollister Incorporated.

All other authors have no conflicts of interest to disclose.

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Prospective Multicenter Evaluation of an Advanced Extracellular Matrix for Wound Management

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ABSTRACT

OBJECTIVE: To evaluate an advanced extracellular matrix made of ovine forestomach matrix (OFM) for healing a variety of wound types.

METHODS: Participants were enrolled from inpatient, outpatient, and home health care settings. The OFM was used to treat all wounds and applied to the wound bed every 3 to 7 days until closure.

RESULTS: Researchers enrolled 29 participants with 33 wounds. Average time to wound closure was 8.2 weeks, the percentage of wounds that reduced in size by 50% or more at 4 weeks was 64%, the average wound area reduction at 4 weeks was 66%, and 73% of wounds had closed at 12 weeks. No adverse effects were observed.

CONCLUSIONS: This represents the first Canadian evaluation of OFM for the treatment of wounds and the positive healing outcomes observed could support more widespread adoption of this matrix.

KEYWORDS: biomaterial, chronic wounds, cellular and/or tissue-based product, extracellular matrix, ovine forestomach matrix, wound healing, wound management

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INTRODUCTION

The dermal extracellular matrix (ECM) in soft tissues is a diverse and heterogenous entity comprising many different proteins and carbohydrates.[1] The appreciation of the role of ECM in all aspects of soft tissue repair has evolved dramatically as understanding of its molecular and biologic complexity has advanced. This intricate network not only provides structural support to the skin but also regulates cellular growth, migration, and differentiation–functions that are vital to tissue repair and wound healing.[2–4] The field of matrix biology has identified roughly 1,000 different proteins collectively termed the matrisome that exist in tissue ECM and play a role in tissue homeostasis and disease.[5] Proteins such as collagen types I, III, and IV, as well as adhesion proteins (eg, fibronectin, laminin) and signaling molecules such as fibroblast growth factor 2, transforming growth factor β,and connective tissue growth factor continuously interact with the cells, which in turn instruct and construct the ECM. This process of dynamic reciprocity underscores the complexity of the ECM, and thus its central role in tissue maintenance.[6]

Acute and chronic wounds are characterized by missing or damaged ECM.[7] In the case of chronic wounds, elevated tissue proteases contribute to the stalled state of these wounds by continuously degrading the ECM, acting against fibroblasts working to reconstruct the skin's scaffold.[2,8] With advances in modern regenerative medicine, missing or damaged ECM can be replaced or augmented by exogenous sources[9,10] such as purified or partially purified xenogeneic decellularized ECM isolated from an appropriate animal species (eg, porcine, ovine, or bovine) or allogeneic ECM from cadaveric sources.[11–13] These new technologies represent a paradigm shift from the traditional reconstituted collagen scaffolds first developed in the 1980's for soft tissue repair and wound management. Reconstituted collagen products, manufactured using a bottom-up approach

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(also referred to as solution phase processing),[14,15] require reformation of the collagen fiber organization to recapitulate the structure found in tissues.[16] In contrast, the preparation of decellularized ECM scaffolds proceeds via a top-down, selective removal of cellular components with a focus on retaining the pre-existing ECM structure, composition, and complexity.[12] In this way, exogenous ECM scaffolds serve as biomimetics of tissue and can faithfully recapitulate ECM biology during the repair process.

One decellularized ECM isolated from ovine forestomach tissue (OFM; Endoform Natural Dermal Template, Aroa Biosurgery, Auckland, New Zealand) is an intact ECM with a composition and structure that closely mimics human soft tissues.[17] This OFM has been shown to retain the native collagen architecture of tissue ECM, with an open porous structure to enable rapid cell repopulation.[18] It contains a large number of matrisome proteins and includes collagens,[19] glycoproteins, signaling molecules, and growth factors.[20] In vitro and in vivo studies have shown that this OFM stimulates cellular differentiation, migration, and the rapid development of vasculature.[17,21] Just like tissue ECM, OFM supports cell proliferation and over time is fully bioabsorbed into the regenerating soft tissue.[21] Further, tissue ECM is an important regulator of the inflammatory response, and the OFM contains components that modulate tissue proteases associated with wound chronicity.[22,23] Accordingly, this OFM has been used extensively in the management of acute and chronic wounds and for complex abdominal wall repair.[24–31]

Like all healthcare systems worldwide, the Canadian system is seeing an increasing number of chronic nonhealing wounds.[32,33] Chronic wounds do not follow a predictable or expected healing pathway, and may persist for months or years despite best practices. The exact mechanisms that contribute to poor wound healing remain elusive; an intricate interplay of systemic and local factors are likely involved. With an ageing population and increased prevalence of chronic diseases, many wounds can be recalcitrant to healing, placing a significant physical, mental, social, and financial burden on the health system as well as individuals living with wounds. Therefore, the aim of this prospective case series was to evaluate the OFM for treatment of acute and chronic wounds across a continuum of Canadian care settings.

METHODS

Informed consent was obtained from all participants. All procedures were performed in accordance with the ethical standards of the respective institutions involved and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Eligible patients who received wound care services in 2018 and 2019 from healthcare facilities including inpatient, outpatient, and home health settings were recruited to represent a cross section of wounds typically managed on a routine basis. In this multisite study, each hospital had a site coordinator who enrolled participants and collected the data. The investigators initially approached potential participants with wounds and obtained consent from those who expressed interest to participate.

Only patients over 18 years of age were included. Exclusion criteria included any medical condition that could compromise healing. Participants who were unwilling to follow the study protocol or could not provide informed consent were excluded from the study.

Treatment Protocol

Aroa Biosurgery supplied the OFM used in this study. Product indications, contraindications, and precautions were followed (Table 1). Prior to application, the OFM was cut to size as needed, then rehydrated in sterile saline or wound exudate. After OFM application, the wounds were dressed using either a nonadherent petrolatum dressing and gauze bandages, antibacterial foam dressing bound with gentian violet and methylene blue (GV/MB; Hydrofera Blue; Hydrofera LLC, Manchester, Connecticut), negative-pressure wound therapy, or absorbent foam (eg, Mepilex, Mölnlycke Health Care, Norcross, Georgia). Compression stockings and appropriate offloading strategies (controlled ankle movement walker boot, offloading padding, and total contact cast) were used as needed. In addition to the OFM, all wounds were managed with local best practice, including debridement during the initial consultation and maintenance of a moist wound environment.

Table 1. STUDY MATRIX INDICATIONS, CONTRAINDICATIONS, AND PRECAUTIONS FOR USE

Indications	Contraindications	Precautions
Partial and full-thickness wounds	Known sensitivity to ovine or collagen material	Uncontrolled clinical infection
Pressure injuries	Third-degree burns	Acute inflammation
Venous ulcers		Excessive exudate
Diabetic ulcers		Excessive bleeding
Chronic vascular ulcers		
Surgical wounds		
Traumatic wounds		
Draining wounds		
Tunneled/undermined wounds		

Source: Aroa Biosurgery Ltd. Endoform Natural Dermal Template, Instructions for Use. August 2018. https://endoform.com/content/uploads/sites/2/2019/04/PI.9103.02-Endoform-Natural-IFU.pdf. Last accessed May 5, 2020.

After the initial consultation, the investigators assessed the wounds every 3 to 7 days. At each visit, the investigators would cleanse the wounds and perform debridement as necessary. Next, the investigators took a photograph of each wound, obtained wound measurements using a paper ruler, and documented the type of wound tissue, including evidence of OFM in the wound. The OFM was reapplied if no residual was present in the wound bed; typically, this was twice weekly for the first 3 to 4 weeks, then weekly as wounds resolved. During the evaluation, the investigators also documented their subjective impressions of the dressing performance based on its fluid handling properties, ease of application, and conformity to the wound using a standardized evaluation tool designed for this study.

Participants were discharged from the study when their wounds achieved 100% re-epithelialization and stopped producing drainage.

Data Analysis

Demographics and outcomes data were prospectively recorded on the patients' medical records then retrospectively extracted from the electronic medical records and entered into an Excel spreadsheet (Microsoft Inc, Redmond, Washington). Wound surface area (cm^2) was calculated by multiplying the longest length (cm) and width (cm) of wound dimensions perpendicular to each other. Percentage reduction in wound area was determined based on the initial wound area. Endpoints measured were the number of healed wounds, average time to wound closure (weeks), and wounds closed at 12 weeks. At 4 weeks, "responder" wounds were defined as those that were 50% or less of the initial wound area. A Kaplan-Meier survival analysis was determined using Excel, and the survival curve used to approximate the number of weeks to achieve closure of 50% of all wounds.

RESULTS

A total of 33 wounds from 29 participants were enrolled in the study. These wounds included venous leg ulcers (VLUs; n = 4, 12%); diabetic foot ulcers (DFUs; n = 8, 24%); pressure injuries (n = 8, 24%); surgical wounds (n = 5, 15%); traumatic wounds (n = 4, 12%); and other wounds (n = 4, 12%) such as pilonidal sinus, necrotizing fasciitis, and radiation-induced injury (Table 2). Fifty-five percent of the participants were male. All wounds were chronic, except one acute surgical wound. During the study, 6 wounds were lost to follow-up, allowing 27 wounds to be followed to closure (Table 2). The average wound duration was 22 weeks (n = 33; range, 0 to 104 weeks; Figure 1A). The average wound size was 20 cm^2 (n = 33), with a range of 0.1 to 165 cm^2 (Figure 1B).

Table 2. PARTICIPANT DEMOGRAPHICS

Demographic	All Wounds (n = 33)	Wounds Followed to Closure (n = 27)
Male:Female, n (%)	16:13 (55:45)	12:11 (52:48)
Wound type, n (%)		
Venous leg ulcer	4 (12)	3 (11)
Diabetic foot ulcer	8 (24)	7 (26)
Pressure injury	8[a] (24)	5 (19)
Surgical	5 (15)	5 (19)
Traumatic	4 (12)	3 (11)
Other	4 (12)	4 (15)
Wound duration,[b] wk, average (range)	22 (0 to 104)	22 (0 to 104)
Wound size,[b] cm^2, average (range)	20 (0.1 to 165)	10 (0 to 61)

[a]Stage III (n = 3), Stage IV (n = 5)
[b]At the start of treatment

According to the evaluation by the investigators the OFM demonstrated excellent handling properties, allowing easy application and conforming well to the wound beds. For deep undermined or tunneled wounds, the OFM could be packed into the defect following rehydration. The OFM required no special handling or storage and could be applied by all those involved in care. No adverse events were reported during the study.

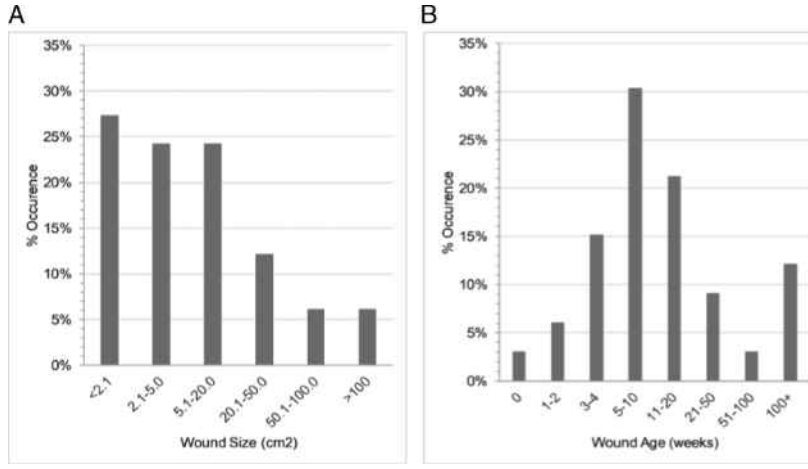
Primary outcomes are shown in Table 3. During the study, six wounds from six participants were lost to follow-up (four at 4 weeks, one at 7 weeks, and one at 11 weeks). The remaining cohort (n = 27) comprised the wounds followed to closure. In this subgroup, the average time to wound closure was 8.2 weeks (range, 2.7 to 19.7 weeks). At 4 weeks, the average percentage wound area reduction was 66% (n = 33, range 4% to 100%). The percentage of all wounds judged closed by 12 weeks was 73% (n = 24/33), or 89% (n = 24/27) when excluding those wounds lost to follow-up. A responder analysis was conducted and showed that at 4 weeks of treatment, 64% (n = 21/33) of all wounds had reduced by at least 50% of the original wound area. The percent of responder wounds increased to 78% (n = 21/27), when wounds lost to follow-up were excluded from the analysis. A Kaplan-Meier survival analysis (Figure 2) was used to estimate the time to closure of 50% of all wounds, 7 to 8 weeks.

CASE SERIES

Case Study 1: Surgical Wound

A 54-year-old female with celiac disease, hypertension, and idiopathic neutropenia underwent previous surgical repair of left knee. The procedure included the removal of the external fixator, open reduction, and internal fixation of the left tibial plateau and shaft, as well as repair of the medial collateral ligament and

Figure 1. A, WOUND SIZE (CM^2) AND B, AGE DISTRIBUTIONS (WEEKS) FOR ALL WOUNDS



medial meniscus, resulting in a nonhealing wound. At the time of intervention, the wound was approximately 8 weeks old and had a layer of dry eschar (Figure 3A). The wound had been previously managed with Polysporin (Johnson & Johnson Inc, New Brunswick, New Jersey). The initial full-thickness wound size was 5.8 x 2.0 cm with 10% slough and 90% granulation tissue (Figure 3B).

Providers conducted a conservative sharp debridement to remove the eschar followed by cadexomer iodine (Iodosorb gel, Smith & Nephew, Watford, United Kingdom) disinfection. The OFM was applied to the wound bed along with a GV/MB foam covering and a light compression sock. Within 2 weeks, the wound size had reduced to 3.8 x 1.7 cm and 100% granulation tissue was achieved (Figure 3D). After 4 weeks of OFM management the wound was closed (Figure 3E).

Case Study 2: Pressure Injury

A 55-year-old male with rheumatoid arthritis sustained a right tibial plateau fracture. A pressure injury to the right anterior ankle with exposed tendon was discovered on removal of the cast. The wound, measuring 2.2 x 1.5 cm, persisted for approximately 4 months and was being managed with standard of care. The OFM treatment was initiated (Figure 4A), covered with GV/MB foam secondary dressing, and underwent weekly dressing changes and re-application of OFM. Within 4 weeks, the wound had begun to reduce in size and granulation tissue had filled the defect and covered the exposed tendon (Figure 4C).

Case Study 3: Full-Thickness Wound

A 67-year-old female presented with profound cellulitis on her left leg and foot resulting in a 6-month blister on

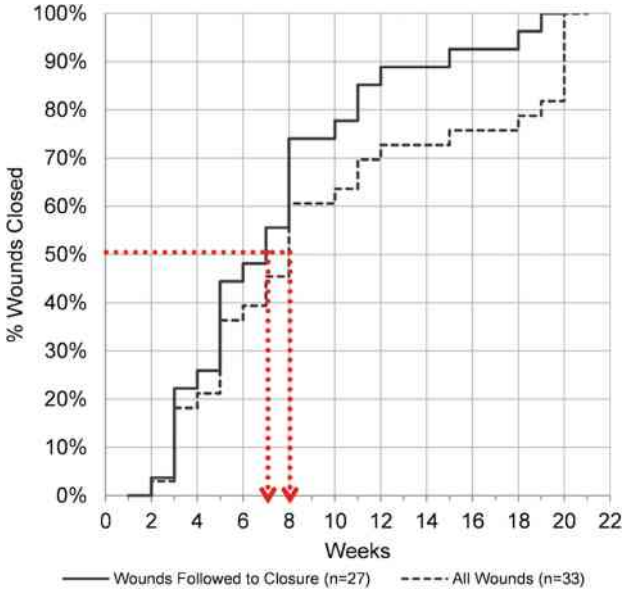
Table 3. STUDY OUTCOMES

Outcome	All Wounds (n = 33)	Wounds Followed to Closure (n = 27)
Wounds closed, n (%)	27 (82)	27 (100)
Average time to closure, wk (range)	N/A	8.2 (2.7 to 19.7)
Wounds closed at 12 weeks, n (%)	24 (73)	24 (89)
Wound area reduction at 4 weeks, % (range)	66 (4 to 100)	65 (4 to 100)
Responders[a] at 4 weeks, n (%)	21 (64)	21 (78)
Venous leg ulcer	2/4 (50)	2/3 (67)
Diabetic foot ulcer	7/8 (88)	7/7 (100)
Pressure injury	3/8 (38)	3/5 (60)
Surgical	5/5 (100)	5/5 (100)
Traumatic	2/4 (50)	2/3 (67)
Other	2/4 (50)	2/4 (50)

[a]≥50% reduction in wound size

Figure 2. KAPLAN-MEIER SURVIVAL CURVE ANALYSIS

All wounds (dashed line, n = 33) and only wounds that were followed to closure (n = 27, solid line). Time to closure of 50% of wounds (7-8 weeks) was estimated based on the survival curves (red dotted line).



the dorsal aspect of foot, which ultimately proceeded to a full-thickness wound (Figure 5A). Previous treatment with a silver barrier dressing (Acticoat, Smith & Nephew) and hydrogel (Intrasite, Smith & Nephew) was unsuccessful. The wound measured 4.6 x 2.7 cm after debridement. The OFM was applied with a GV/MB foam secondary dressing. After 4 weeks, granulation tissue could be observed in the wound bed (Figure 5B) and the patient reported a reduction in pain. The wound continued to reduce in size measuring 4.2 x 2.5 cm, 4.0 x 2.0 cm, 3.0 x 1.8 cm, 2.4 x 1.3 cm, and 2.3 x 1.0 cm on weeks 4 (Figure 5B), 8 (Figure 5C), 10 (Figure 5D), and 11 (Figure 5E), respectively.

Case Study 4: Diabetic Foot Ulcer

A 62-year-old male with type 2 diabetes presented with a 1.3 x 1.0 cm DFU on the fifth metatarsal head of his right foot. The wound had been unresponsive to treatment for 2 months (Figure 6A). Providers initiated wound management with the OFM (Figure 6B) and the wound reduced to 25% of its initial size by week 4 (Figure 6C, 1.2 x 0.3 cm) and closed at week 5 (Figure 6D).

DISCUSSION

Few technologies are available to address the underlying pathology of ECM degradation in chronic wounds, namely excessive tissue proteases. Although some reconstituted collagen dressings can modulate downstream gelatinases and neutrophil elastase,[34,35] the present OFM can modulate

Figure 3. CASE STUDY 1

A, Surgical wound at presentation and prior to debridement with layer of eschar covering the wound bed. B, Postsurgical debridement and prior to initiating management with OFM. C, 3 days after OFM treatment. D, 2 weeks after treatment. E, wound 100% epithelialized at 4 weeks.

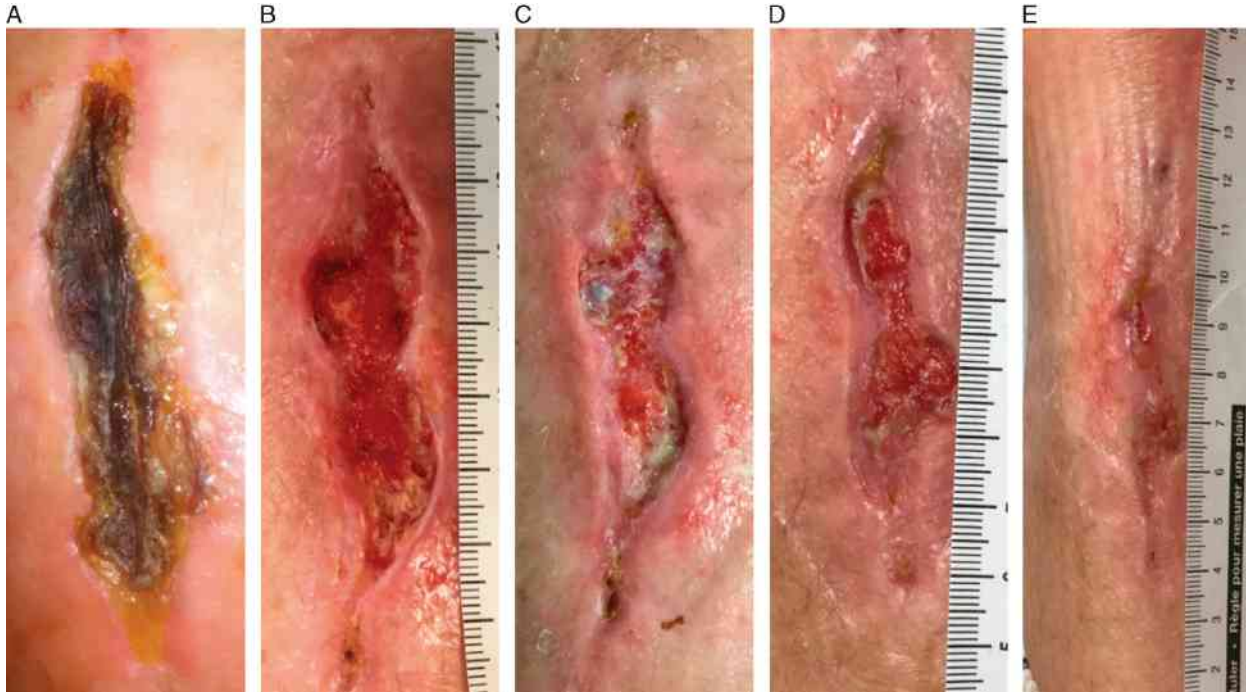
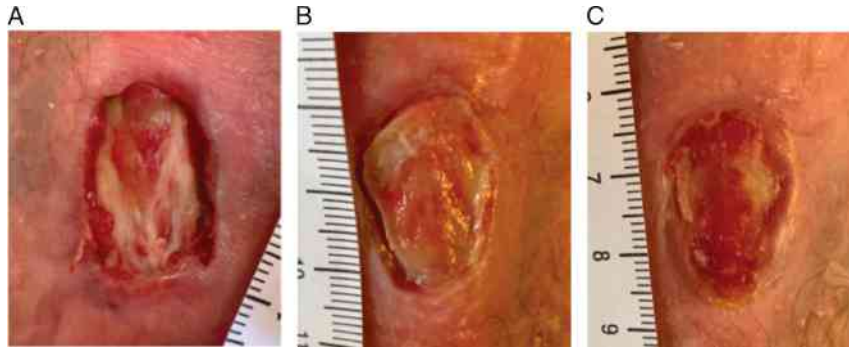


Figure 4. CASE STUDY 2

Management of a pressure injury with OFM. A, Initial presentation of the wound, with exposed tendon. B, week 2 and C, week 4. By week 4, granulation tissue had covered the exposed tendon and filled the defect.



not only the gelatinases but also the collagenases (matrix metalloproteinase [MMP]-1, MMP8, and MMP13), stromelysins (MMP-3 and MMP-10), macrophage metalloelastase (MMP-12), and membrane type I MMP (MMP-12), as well as neutrophil elastase.[22] Recent studies have identified that tissue inhibitors of metalloproteinases are present in OFM,[20] which may in part account for its observed modulatory effect, though based on the complexity of tissue ECM it is highly likely that several modulatory mechanisms are involved. By providing broad-spectrum protease modulation, the OFM works across the enzymatic cascade of collagen degradation rather than simply acting on the down-stream gelatinases. Both tissue ECM and OFM modulate wound proteases while concurrently being degraded by wound proteases. As such, the OFM will have a shorter half-life (persistence) in chronic wounds characterized by elevated protease concentrations relative to wounds that have transitioned to the proliferative phase of healing.

During the course of this study, OFM was often observed as a golden gel present in the wound bed, reminiscent of wound slough. This residual proteinaceous material results from the enzymatic digestion of the OFM in the presence of high protease activity. As the underlying inflammation of the chronic wound was addressed, more residual OFM was seen in the wound bed. The presence or absence of residual OFM material in the wound denotes the inflammatory nature of the wound and can guide the required frequency of material reapplication.[36]

During the proliferative phase of soft tissue healing, exogenous ECMs provide a bioscaffold for cell attachment, migration, and proliferation, leading to the regeneration of the missing or damaged tissue. This OFM can be infiltrated by a variety of cell types and scaffolds tissue repair,[21] a process made more efficient by the retention of native tissue ECM structure and composition.[20] Clinically, investigators observed the formation of well vascularized granulation tissue with concomitant advancement of the epithelial tongue as the OFM scaffolded tissue formation.

Figure 5. CASE STUDY 3

Management of a full thickness wound with OFM. A, week 0; B, week 4; C, week 8; D, week 10; E, week 11.

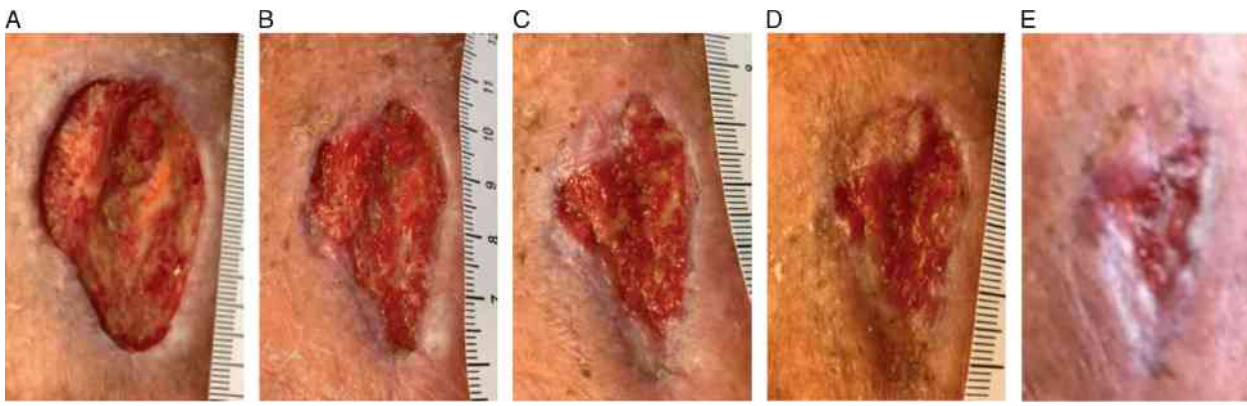
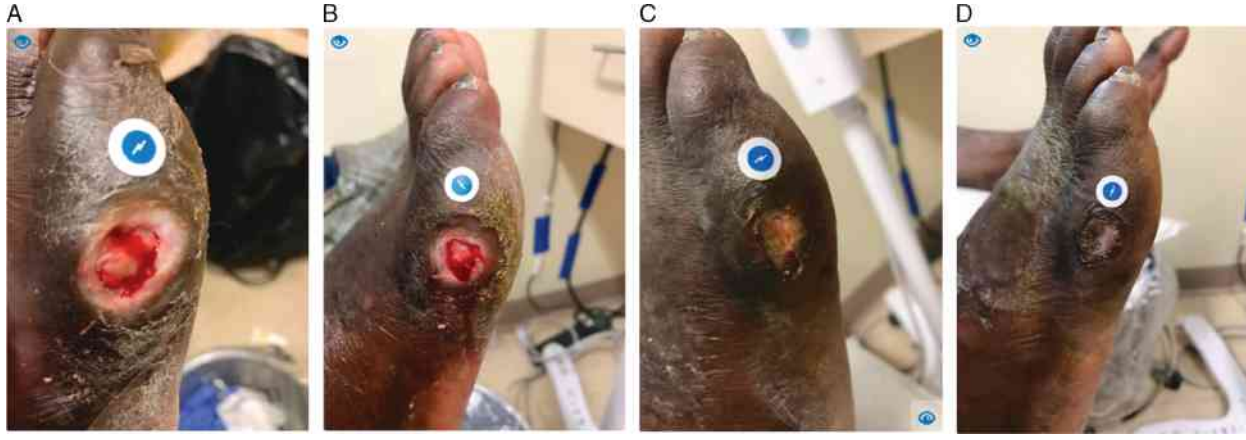


Figure 6. CASE STUDY 4

Management of a DFU with OFM. A, Prior to the initiation of OFM management, wound had been unresponsive to standard of care for 8 weeks. B, week 0 at the initiation of OFM management; C, week 4; D, week 5.



Although advanced ECM technologies have been available for several years to augment tissue proliferation and wound closure, the accessibility of these cellular and/or tissue-based products has limited their adoption in Canada and elsewhere. In contrast, OFM is comparatively affordable,[24,37] making this type of advanced technology accessible to a wider group of wound care patients for the first time. The availability of OFM has enabled a paradigm shift in deploying these types of advanced ECM technologies whereby wounds can now be treated earlier and in a more aggressive fashion to reduce the long-term costs of chronic wounds.[38,39]

The closure rates noted in the current study are comparable with other published studies describing the use of OFM for the management of complex wounds. The incidence of closure at 12 weeks was 89% (n = 24/27) when excluding those lost to follow-up; similarly, Bohn et al[37] observed a 12-week closure incidence of 96% for VLUs (n = 23). Further, Lullove et al[25] and Liden et al[24] observed a 59% (n = 53) and 50% (n = 19) 12-week closure incidence, respectively, using OFM to manage a mix of VLUs, DFUs, and PIs. Ferreras et al[26] observed a 12-week closure incidence of 73% (n = 109) when the OFM was used in conjunction with cellular and/or tissue-based products.

To put these results into perspective, a review of the US Wound Registry determined the 12-week closure incidence using standard of care for DFUs, PIs, and VLUs as 31% (n = 62,964), 30% (n = 66,577), and 44% (n = 97,420), respectively. Published studies using reconstituted collagen dressings such as Promogran (Acelity, San Antonio, Texas) have observed 12-week closure rates of 37% (n = 138) for DFUs[40] and 41% (n = 37) for VLU,[41] whereas Schmitt et al[42] observed only a 1% closure at 12 weeks (n = 60) for VLUs. The overall proportion of responders in the current study was 64% (n = 21/33); in contrast, Gottrup et al[43] observed that 43% of patients responded to treatment with moist gauze (wounds reduced in size by greater than 50% within 4 weeks and predicted to close by 12 weeks).[44]

The quantitative observations made during the study are also reflected in qualitative clinical observations made during treatment. Positive changes in the wound bed were typically noted 2 to 4 weeks following initiation of OFM treatment, such as the initial resolution of underlying inflammation, development of robust granulation tissue, and the advancement of epithelial tissue leading to closure. These clinical observations underlie the clinical performance of the OFM technology transitioning a wound from the chronic stalled state to the proliferative state.

Limitations

Although the results of the current case series are promising, the study does have the typical limitations of an uncontrolled case series including the potential for patient selection bias, lack of comorbidities analysis, lack of a control group, and limited sample size. However, findings from this case series do support a larger comparative controlled study or analysis of a large real-world dataset to understand the relative efficacy of the OFM across various wound types and its potential impact on the economics of wound healing.

CONCLUSIONS

This represents the first Canadian evaluation of the utility of an ovine ECM for the management of chronic wounds. This strategy led to improvements in granulation tissue formation resulting in the resolution of

otherwise stalled chronic wounds. The availability of this advanced technology to Canadian wound specialists provides another tool to manage these complex pathologies. This could be the first step for further Canadian clinical studies and clinical adoption to embed ovine ECM in day-to-day wound management. ●

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ORIGINAL ARTICLE

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Retrospective real-world comparative effectiveness of ovine forestomach matrix and collagen/ORC in the treatment of diabetic foot ulcers

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Abstract

The retrospective pragmatic real-world data (RWD) study compared the healing outcomes of diabetic foot ulcers (DFUs) treated with either ovine forestomach matrix (OFM) (n = 1150) or collagen/oxidised regenerated cellulose (ORC) (n = 1072) in out-patient wound care centres. Median time to wound closure was significantly ($P = .0015$) faster in the OFM group (14.6 ± 0.5 weeks) relative to the collagen/ORC group (16.4 ± 0.7). A subgroup analysis was performed to understand the relative efficacy in DFUs requiring longer periods of treatment and showed that DFUs treated with OFM healed up to 5.3 weeks faster in these challenging wounds. The percentage of wounds closed at 36 weeks was significantly improved in OFM treated DFUs relative to the collagen/ORC. A Cox proportional hazards analysis showed OFM-treated wounds had a 18% greater probability of healing versus wounds managed with collagen/ORC, and the probability increased to 21% when the analysis was adjusted for multiple variables. This study represents the first large retrospective RWD analysis comparing OFM and collagen/ORC and supports the clinical efficacy of OFM in the treatment of DFUs.

KEYWORDS

collagen/ORC, diabetic foot ulcer, ovine forestomach matrix, real-world data, retrospective

Key messages

- a retrospective comparative analysis of healing outcomes in diabetic foot ulcers using real-world data to compare the extracellular matrix technology, "ovine forestomach matrix" (OFM) and a reconstituted collagen, 'collagen/ORC'
- primary outcome of the study was median time to DFU closure (weeks), with secondary endpoints of percentage wounds closed at 12-, 24-, and 36-weeks; and Cox proportional hazards analysis
- the study compared two wound cohorts comprising n = 1150 and n = 1072 DFUs, for the OFM and collagen/ORC cohorts, respectively. OFM-treated DFU had a significantly faster median time to heal; increased percentage of wounds closed (12-, 24-, and 36-weeks), and an increased probability of healing
- this study represents the first large-scale RWD analysis to assess the relative performance of the two technologies in the treatment of DFUs

1 | INTRODUCTION

The successful treatment of diabetic foot ulcers (DFUs) presents multiple challenges for clinicians and incurs a significant psychosocial toll on afflicted patients and their families. In addition to the negative impact on quality of life (QoL) measures, DFUs increase a patient's risk for infection,[1] hospitalisation,[2] and amputation.[3] Current estimates demonstrate one in six patients with a DFU will undergo an amputation, making DFUs the leading cause of nontraumatic amputations in the United States (US).[4] Additionally, there are significant financial burdens incurred by DFUs. A 2012 retrospective study of 7099 DFUs reported a mean cost to achieve closure of $3927 per DFUs.[5]The DFU related cost and burden to the US health care system has been estimated at $9 to 13 billion.[3,6] These factors, coupled with the increasing global incidence of adult type-2 diabetics, presents a significant unmet need in modern healthcare for readily accessible, affordable, and effective interventions for the treatment of DFUs.

Technical and procedural developments in modern wound care have produced numerous advances in the clinical management of DFUs. In parallel, the design of clinical studies to demonstrate therapeutic efficacy has evolved. Real-world data (RWD), as used routinely in other clinical specialties, is a recognised and validated methodology to support real-world evidence.[7,8] Meticulously designed and well-controlled prospective randomised control trials (RCTs), by definition, may not accurately reflect the real-world challenges that clinicians encounter when treating DFUs. For example, a review of 283 published RCTs found that individuals with comorbidities common in the general population were excluded from 81.3% (n = 230) of RCTs.[9] Cohort studies utilising real-world registry data can provide a more compelling and insightful perspective, while minimising bias as compared with RCTs. This is particularly evident in wound care studies where patient variability can be relatively large and RCTs would otherwise exclude patients commonly encountered in the typical Wound Care Centre (WCC). When comparing real-world patient cohorts to RCT cohorts, Fife et al. found that the initial wound area of DFUs selected for RCT studies were three times smaller as compared with the general real-world population.[10] Additionally, the severity of DFUs included in RCTs was not reflective of the typical clinical practice, with 43.6% of real-world DFUs being Wagner 3 or higher, whereas many RCTs only included Wagner 1 and 2.[10] With the exclusion criteria set by RCT's, it is estimated that these types of studies accurately represent only 4% of the real-world wound population.[11] By matching key patient variables across cohort groups, RWD studies may offer clarity regarding the efficacy of specific treatment modalities, enabling meaningful evaluation across significantly larger sample sizes.

For many decades, reconstituted collagen wound dressings have been a commonly used treatment modality for acute and chronic wounds.[12] These traditional technologies are comprised of collagen, isolated from animal tissues (including tendon and hide), using denaturing processes to fully or partially solubilise the collagen, with subsequent downstream fabrication into collagen foams. Many types of commercially available collagen

wound dressings are available, including products comprising 100% reconstituted collagen (e.g., Puracol, Medline Industries), or collagen formulated with natural or synthetic polymers (e.g., oxidised regenerated collagen (ORC), Promogran, 3 M/KCI; carboxymethycellulose, Biostep, Smith and Nephew; or alginate, e.g., Cutimed Epiona, BSN Medical). These reconstituted collagen dressings contain types I and III collagen that rehydrate to a gelatinous form creating a moist environment in the wound bed. More traditional collagen-based dressings have been super-seeded by advanced bioscaffold technologies that support cellular infiltration, migration, and proliferation, providing biological ques to assist in tissue regeneration. One approach in the development of these technologies uses a subtractive manufacturing approach. Starting with a suitable source tissue, cellular components are selectively removed leaving only the proteinaceous tissue extracellular matrix (ECM). These "decellularized extracellular matrix" (dECM)-based technologies retain the structure and composition of soft tissue ECM and have been prepared from numerous source tissues including bovine, equine, porcine, piscine, and cadaveric.[13] Being naturally derived from intact source tissue, dECM products are largely composed of collagen types I and III, but importantly also preserve and contain a diverse array of secondary proteins, polysaccharides, and proteoglycans that are known to play an important role in soft tissue repair through contribution to the milieu of wound healing.[14]

dECM-based products for wound care have largely remained inaccessible because of cost, prescribing habits and insurance coverage, and are therefore typically utilised as a "last resort" in modern wound care, being available only as "cellular or tissue-based product" (CTP, or "skin substitutes"). Ovine forestomach matrix (OFM) (Endoform Natural, Aroa Biosurgery), is the first dECM technology to be made widely accessible to wound care professionals, enabling increased accessibility and adoption into clinical practice. OFM is derived from ovine forestomach tissue using processes optimised to remove ovine cells while maintaining the structure and composition of the tissue ECM.[15] OFM contains more than 150 different proteins, including elastin, fibronectin, glycosaminoglycans and various growth factors, such as vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF).[16] OFM has been shown to recruit mesenchymal stromal cells,[17] stimulate cell proliferation,[18] angiogenesis and vasculargenesis,[18] while modulating wound proteases.[19]

Of the previously mentioned reconstituted collagen dressings, one of the most utilised and studied is the product, collagen/ORC (Promogran, 3 M/KCI). OFM and collagen/ORC are both available for first-line management of wounds. For example, both products are reimbursed in the US as A-code surgical dressings enabling immediate prescription, facilitating incorporation immediately in addition to standard of care (SOC) methods. These two wound care products have similar costs, clinical indications, application techniques, and are used to address wound chronicity (via modulation of wound proteases), support granulation tissue, and advance wound closure in complex soft tissue defects. Our goal was to undertake a retrospective analysis of RWD comparing the relative efficacy of OFM (dECM technology) versus the traditional reconstituted collagen dressing collagen/ORC in the treatment and outcomes of DFUs.

2 | MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki. The study protocol was reviewed by the independent Institutional Review Board (IRB) (Advarra Institutional Review Board Services, MD, USA). The IRB concluded that the study was exempt from IRB approval as the study was retrospective and utilised de-identified wound data.

Data were extracted from the Net Health Wound Care (formerly "Wound Expert") database (NetHealth, Pittsburgh, PA) during the period of January 1, 2014, to June 302 020, representing 449 WWCs across the United States. These are out-patient WCCs that are typically associated with a hospital system and receive patient referrals for specialised care in the management of complex wounds across a spectrum of etiologies and patient demographics. Wounds still under active management at the date of data acquisition were excluded from the study. Data were extracted from a pool of 31 883 wounds (25 762 patients) and filtered based on the inclusion and exclusion criteria represented in Figure 1 and Table 1. The data represented unique visits and associated treatments at the WCC only. Wounds with no baseline characteristics were excluded from the study, as well as wounds that included baseline characteristics but had no follow-up data. Wounds were further filtered based on DFU location and marked "forefoot", "rear foot" or generically 'foot' in the absence of definitive anatomical location. Sequential treatment with either of the products was not specifically assessed in the study; for example, wounds receiving weekly treatment with OFM or collagen/ORC until closure were treated identically to wounds that may have only been treated for a period, then treatment ceased. All wounds were included in the study, including those that had been managed with other advanced therapies; hyperbaric oxygen (HOBT), negative pressure wound therapy (NPWT) and advanced biologic dressings (e.g., CTPs). All patients were assumed to have

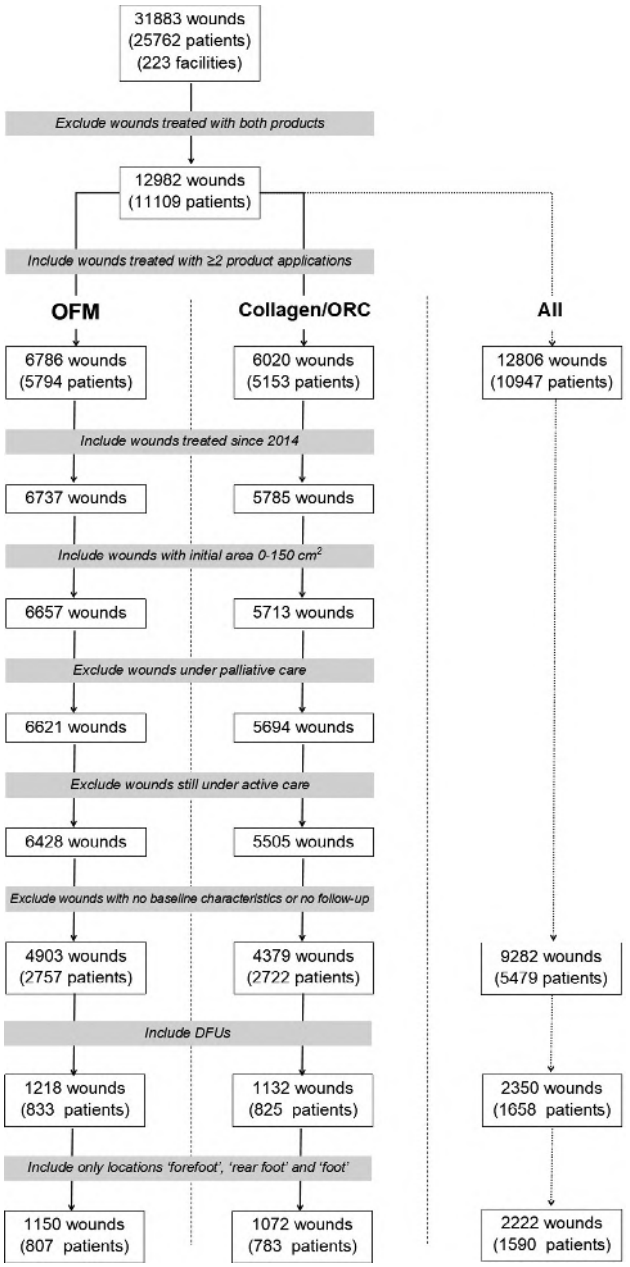

FIGURE 1 Data filtering and sample size (wound and patient) used in the study

had proper offloading (TCC, nonweightbearing, padding) and workup and management of their underlying comorbidities.

Demographic data were summarised by treatment group using mean (standard deviation [SD]) and median for age and frequencies and percentages for gender. Mean blood glucose (eAG) concentrations for each cohort were converted to mean haemoglobin (A1c) using the formula:

$$\mathrm{A1c}(\%) = \frac{\mathrm{eAG}(\mathrm{mg\,per\,dL}) + 46.7}{28.7}$$

TABLE 1 Inclusion and exclusion criteria

Inclusion	Exclusion
• Wounds managed been the period January 1, 2014 to June 30, 2020 • Wound managed with either OFM or collagen/ORC • Diabetic foot ulcer (DFU), with locations marked as "forefoot", "rear foot" or 'foot' • 2 or more applications of the products • Baseline wound area, between 1 and 150 cm^2	• Wounds still under active management • Wounds managed with both products • Patients undergoing palliative treatment • Wounds with follow-up but no baseline characteristics • Wounds with baseline characteristics but no follow-up

Patient demographics were compared between groups using independent *t*-tests and chi-square tests. Wound age was determined from the patient self-reported first incidence of the wound, which did not necessarily correlate with the first placement of either OFM or collagen/ORC. Wound area (cm^2) was calculated from the wound dimensions by multiplying the wound length (cm) and wound width (cm). Baseline wound characteristics including size and wound age, were summarised using mean (SD) and median compared using independent *t*-tests or the non-parametric Mann-Whitney *U* test, as appropriate. The analysis included all DFUs that received 2 or more WCC applications of either product, with a further sub-group analysis for wounds receiving ≥4, ≥8 and ≥12 applications of either product in the WCC.

The number of WCC applications were calculated for all DFUs, as well as for DFUs receiving ≥4, ≥8 and ≥12 applications of either product in the WCC. These data were summarised using mean (SD) and median compared using nonparametric Mann-Whitney *U* test.

Time to closure was defined as the period between the first application of either product and subsequent wound closure, where closure was defined as a wound area of <0.25 cm^2 or where wounds had been marked as "closed", "healed" or "resolved" in the final reporting. The median time to wound closure and the percentage of wounds closed at 12, 24, and 36 weeks were estimated using the Kaplan-Meier method. The percentage of DFUs closed was statistically compared between treatment groups using Greenwood's standard error estimates.

Time to wound closure between the treatment groups was compared using Cox Proportional Hazards (CPH) regression analysis with the comparison summarised as the hazard's ratio (HR) with 95% confidence interval (CI). Adjusted analyses of the time to wound closure were

TABLE 2 Patient demographics

	OFM	Collagen/ORC	*P* value	Total
Patients, n	807	783		1590
Patients, gender specified, n	805	778		1583
Male, n (%)	580 (72.0%)	534 (68.6%)	.137	1114 (70.4%)
Female, n (%)	225 (28.0%)	244 (31.4%)		469 (29.6%
Gender NS, n (%)	2 (0.2%)	5 (0.6%)		7 (0.4%)
Patients, age specified, n	800	708		1508
Mean ± SD (years)	61.8 ± 12.9	62.0 ± 13.0	.725	61.9 ± 12.9
Median (years)	62.0	63.0		62.0
Age NS, n (%)	7 (0.9%)	75 (9.6%)		82 (5.2%)
Patients, glucose specified, n	562	459		1021
A1c, mean ± SD	7.2 ± 3.4%	7.3 ± 3.5%	.930	7.3 ± 3.4%
A1c, median	7.0%	6.9%		6.9%
A1c NS, n (%)	245 (30.4%)	324 (41.4%)		569 (35.8%)

Abbreviations: n, sample size; NS, not specified; SD, standard deviation.

undertaken using CPH regression to compare treatment groups, incorporating age, gender, initial wound size, wound type, and duration of wound as covariates in the model. Adjusted HRs for the treatment group comparison were estimated from these models for the total sample. All analyses performed by using SPSS v26 and a two-tailed *P*-value ≤.05 were taken to indicate statistical significance.

3 | RESULTS

3.1 | Patient demographics

The study followed a pragmatic design, with relatively open inclusion and exclusion criteria. Exclusion criteria consisted of DFUs managed with both products, those still under active management at the time of data acquisition, patients under palliative treatment and wounds with either no baseline characteristics or alternatively no follow-up (Figure 1 and Table 1). Only wounds that received 2 or more WCC treatments with either product, wounds treated since 2014 and wounds with an initial area of 0 to 150 cm^2 were included in the study. A relatively large initial wound area (0-150 cm^2) was included as all wounds were subsequently filtered and verified to ensure only DFUs were included, and wounds had an appropriate anatomic location (e.g., forefoot, foot, or rear foot). Of the initial wound records (n = 31 883), 25 762 patients were filtered (Figure 1) to yield final datasets for the two cohorts for OFM and collagen/ORC of n = 1150 (n = 807 patients) and n = 1072 (n = 783 patients), respectively, that met the study inclusion and exclusion criteria. This represented a total of n = 2222 wounds from n = 1590 patients. Patient demographics for both cohorts are presented in Table 2. The gender mix for the OFM treatment group was not significantly different ($P = 0.137$). OFM treated patients were similar in age ($P = 0.725$) to the collagen/ORC cohort (61.8 ± 12.9 and 62.0 ± 13.0, respectively). Haemoglobin A1c, estimated from the reported patient glucose concentrations (mg/dL) were equivalent between the OFM and collagen/ORC cohorts (7.2 ± 3.4% and 7.3 ± 3.5%, $P = .930$).

3.2 | Baseline wound characteristics

Baseline wound characteristics for the two cohorts are presented in Table 3. Total DFUs (n = 2222) included in the study and receiving ≥2 WCC applications of either product and consisted of 1150 DFUs treated with OFM and 1072 DFUs treated with collagen/ORC. Mean baseline wound areas for the OFM cohort (2.0 ± 5.5 cm^2) were statistically larger ($P = .013$) than the collagen/ORC cohort (1.5 ± 3.8 cm^2), but wounds in both cohorts were of comparable age (15.8 ± 41.7 and 14.5 ± 41.3 weeks, respectively) ($P = .471$). There was no difference in the number of wounds per patient between OFM and collagen/ORC (1.4 ± 0.9 and 1.4 ± 0.8 wounds per patient, respectively). Total wounds could be further segmented based on the number of product applications occurring at the WCC (Table 3), into sub-groups of ≥4, ≥8 and ≥12 WCC applications. Sub-group analyses were undertaken in order to assess the relative efficacy of the products for DFUs that were more challenging to close, hence requiring more visits to the WCC for product application. The

TABLE 3 Baseline wound characteristics

	OFM	Collagen/ORC	*P* value	Total
Baseline wound characteristics (All wounds, ≥2 WCC applications)				
Number of wounds (n)	1150	1072		2222
Mean wound area ± SD (cm^2)	2.0 ± 5.5	1.5 ± 3.8	.013	1.7 ± 4.7
Median wound area (cm^2)	0.6	0.5		0.6
Mean wound age ± SD (weeks)	15.8 ± 41.7	14.5 ± 41.3	.471	15.2 ± 41.5
Median wound age (weeks)	3.9	4.4		4.1
Mean wounds per patient ±SD	1.4 ± 0.9	1.4 ± 0.8	.077	1.4 ± 0.9
Median wounds per patient	1.0	1.0		1.0
Wounds by location (All wounds, ≥2 WCC applications)				
Forefoot (%)	505 (43.9%)	535 (49.9%)		1040 (46.8%)
Rear foot (%)	163 (14.2%)	125 (11.7%)		288 (13.0%)
Foot (%)	482 (41.9%)	412 (38.4%)		894 (40.2%)
Wounds by WCC visit number sub-group analysis				
All wounds (≥2 WCC applications)	1150	1072		2222
≥4 WCC applications	494	475		969
≥8 WCC applications	244	197		441
≥12 WCC applications	155	110		265

Abbreviations: n, sample size; SD, standard deviation.

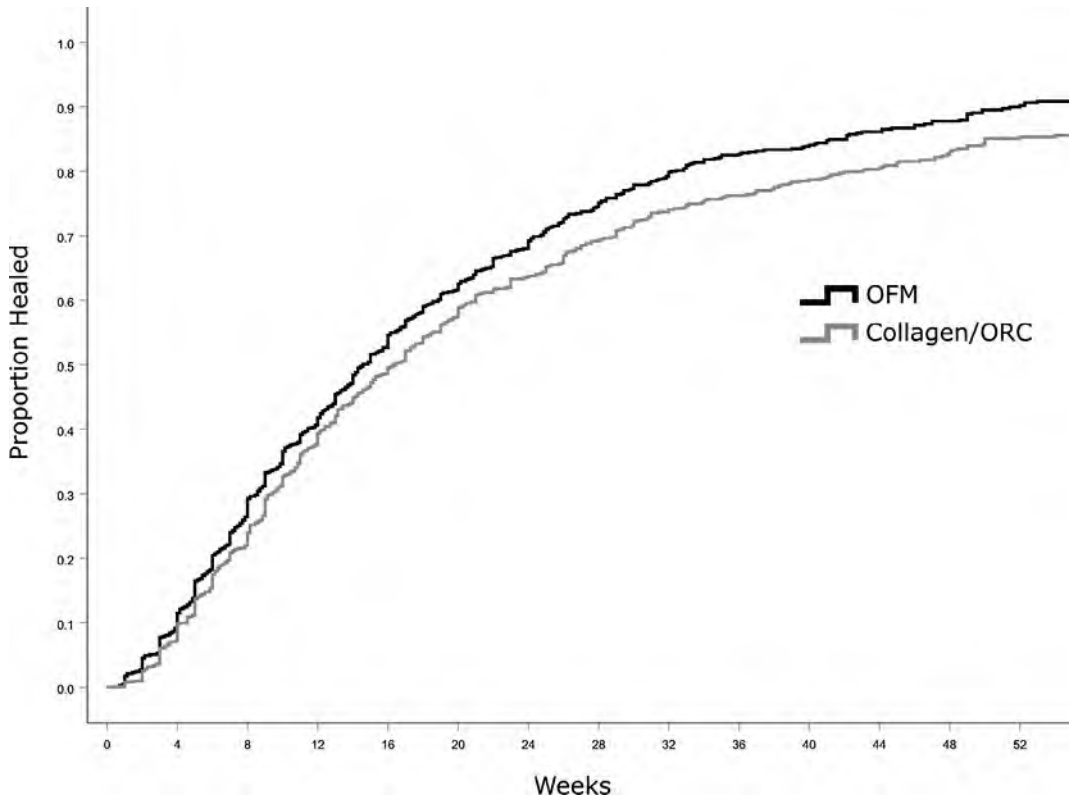

FIGURE 2 Kaplan-Meir survival curves of OFM and collagen/ORC treated wounds (HR = 1.18 [95% CI: 1.06, 1.30], *P* = .002)

smallest sample size for the sub-group analyses were DFUs that received ≥12 WCC product applications with n = 155 and n = 110 DFUs for the OFM and collagen/ORC cohorts, respectively. Comparing the location of the wounds showed a similar distribution between the cohorts, with the majority of DFUs being reported in the forefoot and foot locations.

3.3 | Median healing time

Kaplan-Meir survival curves were generated based on the time to close for wounds in each treatment cohort (Figure 2). Median time to heal was determined based on the Kaplan-Meier method for all wounds receiving ≥2 WCC product applications, and separately sub-group analyses for wounds receiving ≥4, ≥8 or ≥12 WCC applications of either product. Median time to close for all wounds (≥2 WCC product applications) in the OFM cohort were significantly shorter ($P = .0015$) than wounds receiving collagen/ORC, 14.6 ± 0.5 weeks and 16.4 ± 0.7 weeks, respectively (Table 4, Figure 3). This represented a difference in median time to close of 1.9 weeks, or a 11.3% reduction relative to collagen/ORC (Table 4). As expected, as the number of WCC visits and product applications increased, the median time to closure increased for both cohorts as wounds required more weeks of intervention to heal. Additionally, as the number of WCC visits and product applications increased the difference in median time to close between the two cohorts increased. For example, the sub-group that received ≥8 WCC applications of OFM healed 5.6 weeks faster than the collagen/ORC sub-group (20.4 ± 1.3 weeks vs 26.0 ± 2.1, $P = .0118$). For the more challenging wounds captured in the sub-groups receiving ≥8 or ≥12 WCC applications, the median time to close for OFM treated DFUs was reduced by ~20% relative to collagen/ORC.

3.4 | Percentage of wounds closed

The percentage of wounds closed was estimated using the Kaplan-Meir method (Figure 2). The percentage of wounds closed were increased in the OFM cohort at 12-, 24-, and 36-weeks (Figure 4 and Table 4), and these differences were significant at 36 weeks. For example, where wounds received ≥12 WCC applications, 72.5% of OFM treated wounds were closed at 36 weeks versus 57.2% of the collagen/ORC wounds ($P = .0191$).

TABLE 4 Median time to close and percentage of wounds closed

	OFM	Collagen/ORC	Difference	*P* value	Overall
Median time to close (weeks ± standard error)					
All wounds (≥2 WCC Applications)	14.6 ± 0.5	16.4 ± 0.7	1.9 (11.3%)	.0015	15.3 ± 0.4
≥4 WCC applications	18.1 ± 0.9	21.0 ± 1.8	2.9 (13.6%)	.0040	19.9 ± 0.9
≥8 WCC applications	20.4 ± 1.3	26.0 ± 2.1	5.6 (21.4%)	.0118	23.0 ± 1.3
≥12 WCC applications	22.0 ± 2.1	27.3 ± 4.2	5.3 (19.4%)	.0355	24.0 ± 2.0
Percentage of wounds closed, 12 weeks [95% CI]					
All wounds (≥2 WCC applications)	40.6%[37.7%, 43.6%]	37.6%[34.6%, 40.7%]		.1695	
≥4 WCC applications	27.5%[23.4%, 31.6%]	26.0%[21.9%, 30.1%]		.6093	
≥8 WCC applications	22.4%[17.1%, 27.8%]	23.5%[17.5%, 29.5%]		.8011	
≥12 WCC applications	23.8%[17.0%, 30.6%]	20.5%[12.9%, 28.2%]		.5272	
Percentage of wounds closed, 24 weeks [95% CI]					
All wounds (≥2 WCC applications)	68.0%[64.9%, 71.0%]	63.6%[60.3%, 66.9%]		.0571	
≥4 WCC applications	59.3%[54.5%, 64.0%]	52.5%[47.6%, 57.3%]		.0500	
≥8 WCC applications	55.4%[48.7%, 62.1%]	45.3%[38.0%, 52.6%]		.0468	
≥12 WCC applications	53.1%[44.8%, 61.4%]	42.4%[32.8%, 51.9%]		.0961	
Percentage of wounds closed, 36 weeks [95% CI]					
All wounds (≥2 WCC applications)	82.5%[79.8%, 85.2%]	76.2%[73.1%, 79.4%]		.0033	
≥4 WCC applications	76.9%[72.5%, 81.3%]	67.3%[62.4%, 72.2%]		.0046	
≥8 WCC applications	73.6%[67.3%, 80.0%]	60.8%[53.2%, 68.4%]		.0113	
≥12 WCC applications	72.5%[64.7%, 80.3%]	57.2%[47.0%, 67.3%]		.0191	

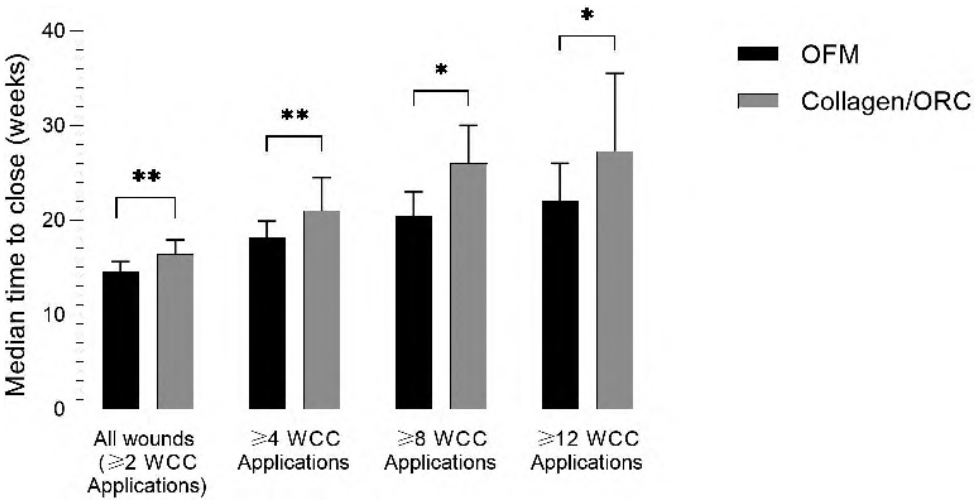

FIGURE 3 Median time to wound closure. Error bars represent upper and lower 95% confidence intervals. ns, not significant; *$P < .05$; **$P < .01$; ***$P < .001$

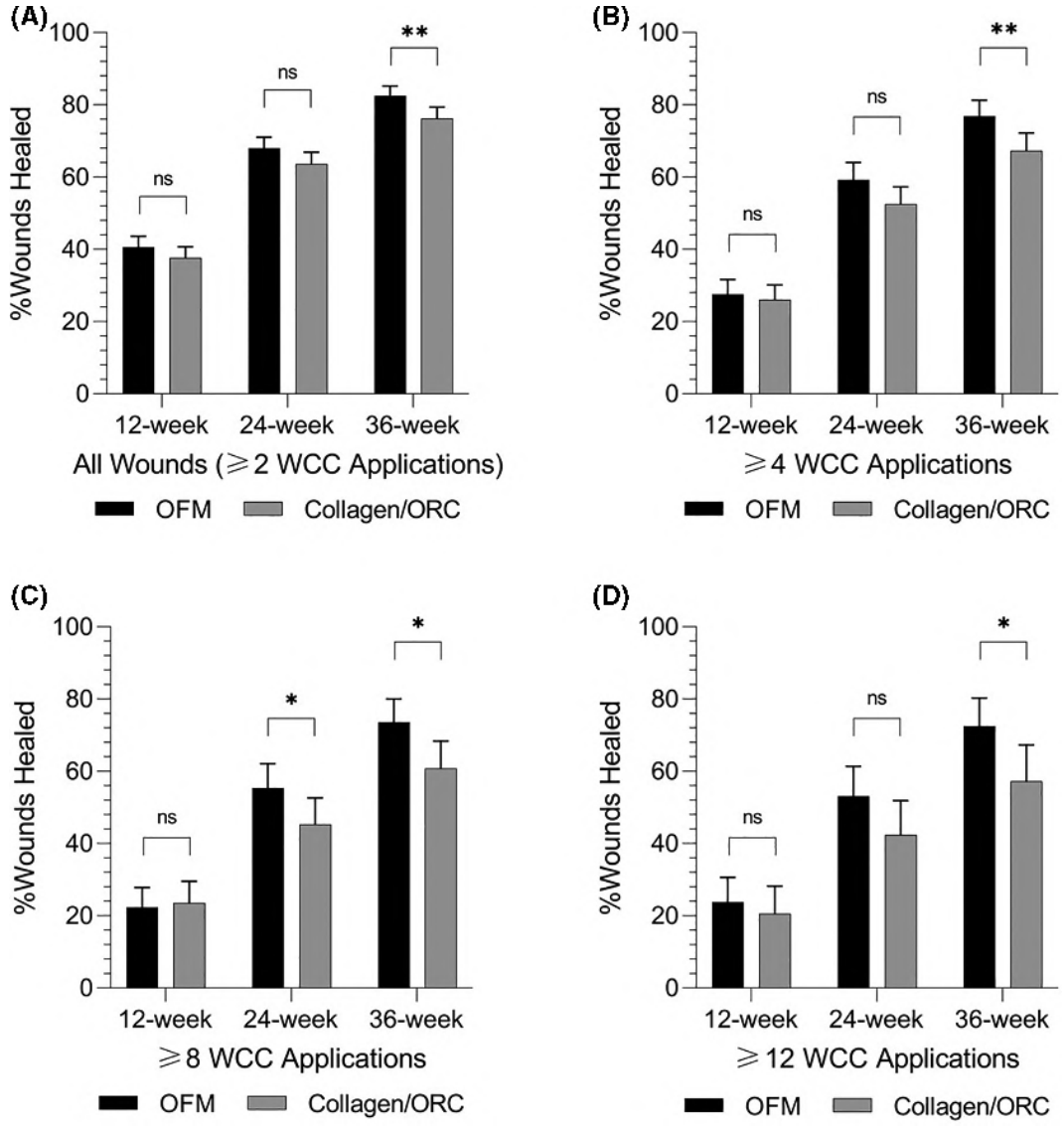

FIGURE 4 Percentage of wounds closed. Error bars represent upper and lower 95% confidence intervals. ns, not significant; *$P < .05$; **$P < .01$; ***$P < .001$

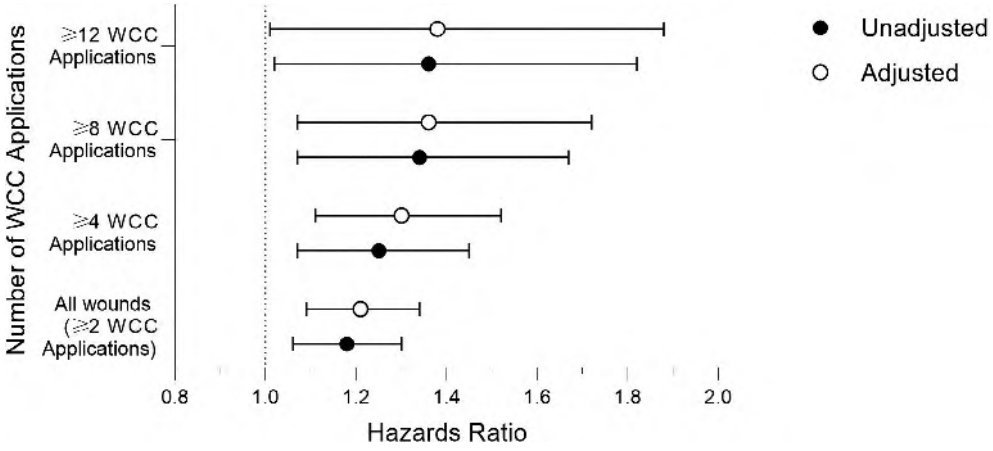

FIGURE 5 Forest plot of Hazards ratios (HR) from unadjusted and adjusted CPH analysis. Error bars represent that upper and lower 95% CI. Dotted line represents HR = 1.0

TABLE 5 CPH regression analysis

	Unadjusted	*P* value	Adjusted	*P* value
All wounds (≥2 WCC applications)	1.18[1.06, 1.30]	.001	1.21[1.09, 1.34]	.0004
≥4 WCC applications	1.25[1.07, 1.45]	.004	1.30 [1.11, 1.52]	.001
≥8 WCC applications	1.34[1.07, 1.67]	.012	1.36[1.07, 1.72]	.012
≥12 WCC applications	1.36[1.02, 1.82]	.036	1.38[1.01, 1.88]	.045

Note: Hazard ratios [95% CI].

TABLE 6 Product applications

	OFM	Collagen/ORC	*P* value	Overall
All wounds (≥2 WCC applications)				
Mean ± SD	6.8 ± 16.3	5.5 ± 8.6	.257	6.2 ± 13.1
Median	3.0	3.0		3.0
≥4 WCC applications				
Mean ± SD	13.4 ± 23.2	10.1 ± 11.3	.019	11.8 ± 18.4
Median	7.0	6.0		7.0
≥8 WCC applications				
Mean ± SD	22.0 ± 30.8	17.2 ± 14.8	.059	19.9 ± 25.0
Median	14.0	12.0		13.0
≥12 WCC applications				
Mean ± SD	29.5 ± 36.6	23.4 ± 17.5	.073	30.3 ± 19.0
Median	20.0	17.5		19.0

3.5 | Cox proportional hazard (CPH) analysis

The time to wound closure were further analysed using CPH regression to compare treatment groups and to identify differences as the number of WCC visits and product applications increased. Without adjustment, the OFM cohort had a 18% greater probability of wound closure compared with the collagen/ORC cohort ($P = 0.001$) (Figure 5 and Table 5). When the adjusted CPH model incorporated age, gender, initial wound size and wound age the adjusted hazards ratios represented a 21% greater probability of wound closure for the OFM cohort ($P = .001$). When sub-divided by number of WCC applications the OFM treatment significantly increased the probability of wound closure by up to 36% and 38% in the unadjusted and adjusted models (Figure 5 and Table 5).

3.6 | Number of product applications

The mean number of WCC reported product applications for all wounds (≥2 WCC applications) were 6.8 ± 16.3 and 5.5 ± 8.6 applications for OFM and collagen/ORC cohorts, respectively (Table 6). The number of product applications was further analysed based on the sub-groups ≥4, ≥8, and ≥12 WCC applications. There were no significant differences between the cohorts with respect to the mean product applications, except for the sub-group receiving ≥4 WCC applications, where the mean number of OFM applications (13.4 ± 23.2 applications) was higher than the collagen/ORC sub-group (10.1 ± 11.3 applications) ($P = .019$).

4 | DISCUSSION

In this retrospective RWD study, 2222 DFUs were sourced from 223 facilities and 1508 patients (Figure 1). The primary study outcome was median time to wound closure; DFUs treated with OFM closed significantly faster (14.6 ± 0.5 weeks) compared with the collagen/ORC cohort (16.4 ± 0.7 weeks), a difference of 1.9 weeks. As the number of WCC product applications increased the difference between the median time to closure increased. For example, the median time to closure of the OFM sub-group receiving ≥8 WCC applications was 5.6 weeks shorter than the collagen/ORC sub-group (Table 4). OFM treated DFUs had a higher percentage of wound closure at 12-, 24- and 36-weeks (Table 4), that was statistically significant at 36-weeks, and an increased the probability of healing by up to 38% (Table 5). A previous published RCT comparing the efficacy of collagen/ORC to SOC in the treatment of DFUs reported a 12-week incidence of healing of 37.0%, consistent with our findings (37.6%, Table 4).[20] It is interesting to also compare these findings to the large retrospective analysis of RWD taken from the US Wound Registry that determined the percentage of DFUs closed at 12 weeks using SOC alone was ~30%.[10]

The data captured by the EMR reflect only those visits to the outpatient WCC, and as such, wound parameters (e.g., area) and associated treatments at interim dressing changes outside the WCC (e.g., home health) are not reflected. While this limitation does not necessarily impact the overall reporting of the healing outcomes (e.g., median time to close, percentage of wounds closed), product applications are only reported for the WCC visits. This is especially important when considering the number of product applications. Across all DFUs, the mean number of product applications for OFM and collagen/ORC were 6.8 ± 16.3 and 5.5 ± 8.6, respectively, with a median of 3.0 product applications for both cohorts (Table 6). However, this underestimates the actual product usage for the collagen/ORC group. Collagen/ORC becomes a gel in the wound bed, and as such must be re-applied every 2 days, or daily in the case of moderately exudating wounds.[21] Thus, actual clinical usage of collagen/ORC are likely to be up to seven times greater than the application rates reported in Table 6. In comparison, OFM remains in the wound bed for up to 7 days depending on the chronicity of the wound and associated concentrations of wound proteases. Several studies have described tailoring the re-application of OFM to match wound chronicity, typically starting treatment with twice weekly re-application for the first 2 to 4 weeks, then reducing the re-application frequency to weekly as wound chronicity is corrected.[22,23] As WCC visits typically occur weekly, the OFM application rates presented in Table 6 are expected to approximate actual clinical usage.

There is a growing body of evidence to support the use of OFM in healing a variety of wound types.[22-28] However, to the authors' knowledge there has not been a large, retrospective RWD study of OFM making comparisons to a reconstituted collagen product. In this instance we selected collagen/ORC for the comparison given the products long-established use in wound care. A related study used RWD to compare the efficacy of OFM to collagen/ORC/silver.[29] However, it is difficult to compare findings from this study with our own, as most notably, the study compared OFM to a silver-based antimicrobial collagen dressing. The antimicrobial properties of silver are well known in wound care and, further, the detrimental impact of bacterial contamination and biofilm on wound healing is well understood.[30-32] As such, it is difficult to draw any conclusions from a study comparing two products with different mechanisms of action. Additionally, the study did not assess changes in wound area or wound closure, but instead utilised non-traditional outcome measures.[29]

The argument that all collagen-based devices are not the same has been well documented and highlights differences between the semi-synthetic reconstituted collagen type products and dECM bioscaffolds.[33-35] While both OFM and collagen/ORC are readily accessible for modern wound care, there are significant differences in composition. OFM contains over 150 different proteins that naturally occur in tissue ECM, including a variety of growth factors,[16] while collagen/ORC comprises only oxidised regenerated cellulose (ORC) and 55% type I bovine reconstituted collagen.[36] These compositional differences have been demonstrated to result in measurable differential performance outcomes. Comparative in vitro testing of OFM has demonstrated greater cellular bioactivity,[18] more potent inhibition of relevant wound proteases[19] and greater retention of native matrix structure,[37] relative to collagen/ORC.

As a dECM, OFM represents a newer class of advanced wound care technology that have otherwise had limited clinical adoption because of financial barriers. The main feature of these tissue derived products, also termed CTPs, is the preservation and inclusion of secondary ECM proteins, particularly growth factors and additional signalling molecules that aid and promote healing. As the only dECM technology that is widely available for the day-to-day management of acute and chronic wounds, OFM represents a step change in the accessibility of these types of technologies to a wider patient population. For example, OFM and collagen/ORC are similarly priced at $USD 8-12/unit, while alternate dECM products, available as CTPs command prices of up to $1000 to $2000/unit. Where CTPs have traditionally only been used in wounds that have failed to respond after 4 to 8 weeks of SOC treatment, OFM can be initiated much earlier in the continuum and integrated into SOC. An additional benefit of being an "A-code" surgical dressing is the ability for OFM to be prescribed for US patients through a Durable Medical Equipment (DME). Globally, given the ease of application, the product can be applied by patients, caregivers, or home health care providers. The "proactive and early, aggressive"' utilisation of OFM, along with optimal wound bed preparation and secondary treatment modalities to disrupt the pathophysiology of chronic wounds was first proposed by Bohn et al[38] as a protocol to improve wound closure rates. In the pragmatic design of this study, we have been deliberate in not defining inclusion/exclusion criteria to preclude DFU managed with additional advanced wound therapies, for example, hyperbaric oxygen therapy, negative pressure wound therapy, and CTPs. This approach was taken so as to not imply that OFM could replace any of these advanced therapies, but rather serves as a synergistic adjunctive therapeutic option in the armament of wound care professionals. For example, Ferreras et al demonstrated that while upfront management with OFM to correct wound chronicity reduced CTP usage, importantly, this approach also improved overall healing outcomes when CTPs were utilised later in the continuum.[28]

Our findings demonstrate that OFM can reduce the time of DFU closure by up to ~20% relative to collagen/ORC. This outcome has significant implications for patient QoL, but it is also valuable to consider the financial implications for other key stakeholders across the continuum of care. For patients, this represents a direct savings of up to ~20% incurred for any out-of-pocket expenses relating to their treatment including insurance co-payments, loss of income because of time off work or additional treatment related costs (e.g., transportation expenses).[39] One consistent finding from the literature is that the main contributor to the overall cost to wound closure is professional time related to dressing changes, while material costs (e.g. primary and secondary dressings, saline, offloading pads) comprise ~10% of total cost.[5,40,41] Thus, a significant reduction in the median time to wound closure could have direct positive impacts for payors, private insurers, and/or government agencies by reducing the total cost to wound closure. It is also important to consider those sites of care (e.g., Home Health Agencies) that receive a bundled payment for each episode of care. In these instances, reducing the time to wound closure by ~20%, or increasing the probability of closure by up to 38%, improves the likelihood that expenses incurred during wound treatment will not exceed the payment cap. In an era of increasing pressure on healthcare systems to remain financially viable, reducing the time to wound closure improves efficiency and productivity by increasing the number of new patient encounters, while maintaining resource allocation near neutral. New patient encounters have a positive impact on the financial health of a facility by enabling downstream revenue associated with new consultations. For example, new consultations undergo initial evaluation and management (E/M), wound debridement as well as advanced interventions, for instance diagnostic and interventional arterial and venous procedures or HOBT.

4.1 | Limitations

By undertaking a large retrospective RWD study, we have been able to compare the relative efficacy of OFM and collagen/ORC across a significantly large number of wounds representing a complex patient demographic using previously defined recommendations.[42,43] As with other RWD studies, a limitation is that EMR databases are not typically developed for retrospective research purposes so there is inherent variability in the day-to-day documentation practices. Uniform data reporting is not typically monitored leading to the potential for inconsistent or "Missing Completely at Random" (MCAR) data. In this study, MCAR data would include fasting glucose readings, plantar or dorsal wound location, use of total contact casts (TCCs), adjunctive vascular intervention, and patient demographics (e.g., age, gender). One approach to potentially control for MCAR and other RWD reporting variability is to use matched-cohorts whereby treatment groups are carefully selected to identify two statistically equivalent cohorts. In this current study we instead used a pragmatic approach to derive two cohorts that were essentially equivalent based on demographics and baseline wound characteristics. Rather than using matched cohorts, adjusted CPH analysis using key variables (e.g., wound age, wound size) were used to

offset any differences between the two cohorts. RWD analysis also assumes that each patient had a proper diagnostic workup and any intervention to optimise healing. This limitation though is assumed to be controlled for as there are multiple guidelines on the recommendations for revascularization requirements, offloading, treatment of infections, metabolic control, and local ulcer care.[44,45]

5 | CONCLUDING REMARKS

This retrospective RWD analysis demonstrates that the use of OFM reduced the median time to closure, increased the percentage of wounds closed, and increased the probability of closure relative to wounds managed with collagen/ORC. Differences between OFM and collagen/ORC were most apparent for wounds that required a greater number of WCC visits. This RWD study further substantiates the growing body of evidence to support the use of OFM as a first-line intervention to improve wound closure rates.

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CONFLICT OF INTEREST

BB, SGD and BCHM are employees of Aroa Biosurgery Limited (Auckland, New Zealand). BCHM is a shareholder of Aroa Biosurgery Limited. TM is an employee of Net Health (Pittsburgh, Pennsylvania). AEC, GAB, KW, BDL, MMM have received educational grants from Aroa Biosurgery Limited. CF, CDL and TM provided consulting services to Aroa Biosurgery Limited.

DATA AVAILABILITY STATEMENT

Data subject to third party restrictions. The data that support the findings of this study are available from Net Health. Restrictions apply to the availability of these data, which were used under license for this study. Data are available Net Health with the permission of Net Health.

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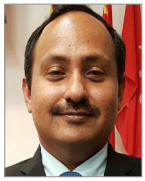
Use of an advanced extracellular matrix dressing in the treatment of acute and chronic wounds: a Malaysian case series



Chronic wounds are becoming an increasing burden on healthcare systems as the Malaysian population develops more complex comorbidities. These wounds present a challenge for health professionals to treat without having access to advanced wound healing technologies that have not been available in Malaysia. We report a retrospective case series (n=10) detailing one Malaysian wound care centre's initial experience with a novel decellularised extracellular matrix, ovine forestomach matrix (OFM), used in the treatment of both acute and chronic wound. At the 12-week mark, the principal investigator deemed 90% (9/10) wounds to be closed or improving.

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There is an ever-growing need for advanced wound care products in Southeast Asia as the region begins to see a dramatic rise in chronic wounds (Norman et al, 2020). In a 2015 survey assessing the rate of diabetes in Malaysia, it is estimated that 2.8 million (20.8%) Malaysians have type II diabetes (Hussein et al, 2016). It has been well documented that approximately 25% of patients with diabetes will sustain a wound over the course of their lives (Price, 2004; Singh et al, 2005) and these wounds are notoriously difficult to close due to the chronically inflamed wound environment (Spampinato et al, 2020). At present the standard of care for chronic wounds typically focuses on managing the symptoms of the wound (e.g., exudate and pain) rather than addressing the underlying wound pathophysiology to accelerate the wound healing process. With an increasing proportion of the Malaysian population becoming high risk for sustaining a chronic wound there is a growing demand for cost-effective technologies to achieve wound closure.

Recent advances in the field of regenerative medicine have identified tissue-based extracellular matrix (ECM) as a broad class of technology that can scaffold soft tissue regeneration and are particularly suited to wound repair (Pradhan et al, 2009; Gould, 2016). These products are not synthetic, but rather tissue-derived, being isolated from intact mammalian tissues using processes to remove cellular components while keeping the structure and biology of the ECM intact (Gould, 2016). When placed in the wound bed, these products scaffold cellular infiltration and enhance the body's natural ability to heal. While these types of technologies have been widely available and readily adopted in many health care systems, global uptake has been slow due to economic barriers. For example, ECM-based technologies have not traditionally been available to Malaysian wound care professionals. Decellularised extracellular matrix derived from ovine forestomach, termed ovine forestomach matrix (OFM) is one of these ECM-based products. OFM acts as a scaffold to aid host cell migration and proliferation, and over time OFM is fully integrated into native tissue (Overbeck et al, 2020). OFM contains naturally occurring ECM proteins that provide structure to the site of injury and key resources for the regenerating tissue at different stages of healing (Lun et al, 2010). During the inflammatory phase, OFM modulates the innate immune response (Street et al, 2015) and modulates proteases leading to resolution of wound chronicity (Negron et al, 2012). During the proliferative phase of healing, OFM interacts with rebuilding cells such as mesenchymal stem cells, fibroblasts, endothelial cells and keratinocytes (Lun et al, 2010, Irvine et al, 2011, Dempsey et al, 2020) by providing a structural support for these cells and releasing

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Key words:

- *Ovine forestomach matrix*
- *Chronic wounds*
- *Wound care*
- *Case series*

Table 1.

Sex/age	Comorbidities	History	Wound age (weeks)	Wound area (cm^2)	Outcomes
M, 67	DM, HTN, HDL	Gangrene and 2nd toe amputation	8	76.5	Healed at 10 weeks
M, 70	DM	DFU with cellulitis	2	14.0	Improvements in granulation tissue at 4 weeks
M, 82	CHF, HTN, BPH	Lower leg ulcer	55	3.0	Improvements in granulation tissue at 15 weeks
M, 66	DM	3rd toe amputation	12	7.5	Healed at 3 weeks
F, 65	DM, HTN	Lower leg ulcer with prior cellulitis	68	15.0	Improvements in granulation tissue at 15 weeks
F, 58	DM, HTN	Surgical saucerisation of a carbuncle	48	9.0	Improvements in epithelial tissue at 7 weeks
M, 4	NKMI	Traumatic laceration with exposed fascia	2	18.0	Palmar fascia coverage at 1 week. Fully granulated after 4 weeks
M, 29	DM, HTN	Non healing ulcer post TMA	104	1.8	Healed at 2 weeks
M, 33	NKMI	Postoperative fasciotomy for compartment syndrome	36	24.0	Minimal change
M, 63	DM, HTN	Recurrent VLU	212	21.0	Improvements in granulation tissue at 5 weeks

M=male; F=female; DM=diabetes mellitus; HTN=hypertension; HDL=hyperlipidemia; CHF=congestive heart failure; BPH=benign prostate hypertrophy; NKMI=no known medical issues; TMA=trans-metatarsal amputation; VLU=venous leg ulcer

biologically active proteins that encourage the formation of granulation tissue, vasculature and ultimately new tissue ECM.

OFM has recently been made available in Malaysia for the management of acute and chronic wounds. This retrospective case series describes our early experience and clinical outcomes using OFM to treat wounds from the Malaysian patient population.

Materials and methods

As part of standard treatment, all patients provided written informed consent for their images and data to be used for research purposes. The study was conducted in accordance with World Medical Association Declaration of Helsinki ethical guidelines. Relevant de-identified patient data was collated retrospectively, along with wound images. As this was a pilot evaluation of a new technology no inclusion or exclusion criteria were defined for patient selection.

The case series was conducted at a single wound care centre. Upon presentation at the clinic, all patients underwent an initial debridement of non-viable tissue. If the patient was identified by the principal investigator to be a suitable candidate for OFM (Endoform™ Natural Dermal Template, Aroa Biosurgery Limited, Auckland, New Zealand), it was placed into the wound bed, hydrated with a normal saline and wound exudate and allowed to adhere to the wound bed. The OFM was then covered with a non-adherent contact layer covered with an appropriately sized foam secondary dressing. All patients were instructed

to abide by the institutional guidelines for proper offloading, compression and/or use of any adjunctive therapies. Patients were seen once weekly in the wound care clinic for repeat applications of OFM and would undergo debridement at the clinician's discretion. All measurements were recorded using a paper ruler and digital photography was used to capture all wounds.

Results

A total of ten wounds were included in this case series, with one patient lost to follow-up during treatment *(Table 1)*. The majority of patients were male (8/10), and the mean patient age was 53.7 years old. The aetiology of the wounds consisted of surgical wounds, diabetic foot ulcers (DFU), venous leg ulcers (VLU), and traumatic wounds *(Table 1)*. Mean wound age at presentation was 55 weeks (range: 2–212 weeks) and mean baseline wound size was 19cm^2 (range: 1.8–76.5cm^2). Wounds received treatment with OFM for up to 20 weeks. At the time of data collection, the principal investigator (HKRN) judged 90% (n=9) wounds had achieved either complete closure or improvement from the initial baseline status. The average percent area reduction at four weeks was 57%, with five wounds achieving at least 50% area reduction by four weeks.

Here we will present four examples of patients who received OFM as a part of their treatment regimen. The four examples highlight how OFM can be used to treat both acute and chronic wounds.

Case 1

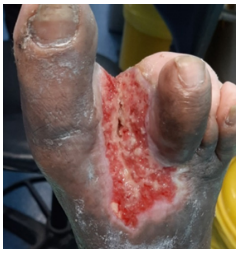
A 67-year-old male with a past medical history of diabetes mellitus, hyperlipidaemia and hypertension presented to the clinic with an 8-week-old wound from a surgical dehiscence of a right foot 2nd toe amputation for gangrene *(Case 1a)*. At the initial visit, the wound measured 17.5 cm x 4.5cm after the initial debridement of non-viable tissue. OFM was hydrated with saline and wound exudate upon application to the wound bed. This was followed by a non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap. The patient was instructed to properly offload the right foot and was given assistive devices to allow for this accommodation. The patient was instructed to change their foam dressing every three days with repeat application of OFM occurring at each weekly clinic visit. By week two the wound had begun to contract slight measuring 16.5 x 3.5cm and had a healthy bed of granulation tissue *(Case 1b)*. By week 8 the wound had closed to 0.1 x 0.1cm *(Case 1c)* and by week 10 was completely reepithelialised with no drainage or dressing changes required *(Case 1d)*.

Case 2

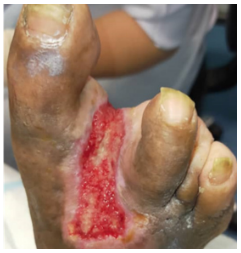
A 66-year-old male with a past medical history significant for diabetes mellitus presented to the clinic with a 12-week-old wound from a left 3rd toe resection for gangrene. At the initial visit, the wound measured 5 x 1.5cm after the initial debridement of non-viable tissue *(Case 2a)*. OFM was hydrated with saline and

Case 1. Surgical wound dehiscence following a toe amputation gangrene.

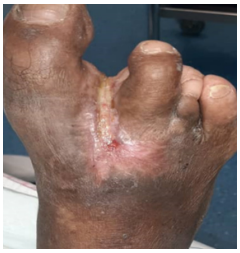
- A 67-year-old male with diabetes mellitus, hyperlipidaemia and hypertension and a 8-week-old wound from surgical wound dehiscence of a right foot 2nd toe amputation for gangrene
- On application to the wound bed OFM hydrated with saline and wound exudate and covered with non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap
- The patient was instructed to change their foam dressing every three days. Application of OFM occurring at each weekly clinic visit
- By week 10 was completely reepithelialised.



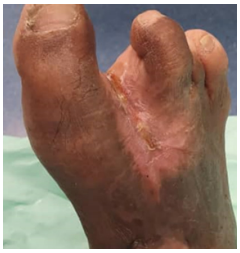
a. Initial defect, measuring 17 x 4.5 cm



b. 2 Week follow up, defect measuring 16.5 x 3.5cm



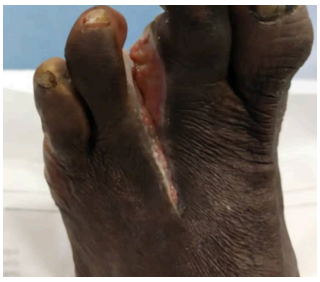
c. Week 8 follow up, defect measuring 0.1 x 0.1cm



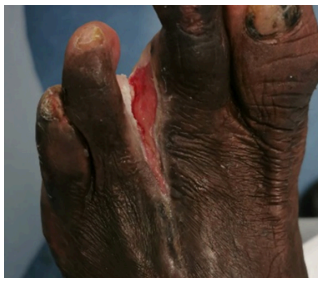
d. Week 10, 100% reepithelialised

Case 2. Wound caused by a toe resection for gangrene.

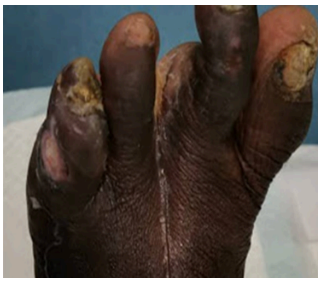
- A 66-year-old male with diabetes mellitus and a 12-week-old wound from a left 3rd toe resection for gangrene
- On application to the wound bed OFM hydrated with saline and wound exudate and covered with non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap
- The patient was instructed to change their foam dressing every three days. Application of OFM occurring at each weekly clinic visit
- Complete closure had occurred by the three-week visit.



a. Initial defect, measuring 5 x 1.5cm



b. Week 1 follow up visit, defect measuring 4.0 x 1.0cm



c. Week 3 follow up, defect 100% reepithelialised

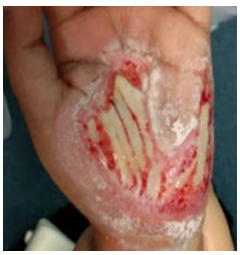
wound exudate upon application to the wound bed. This was followed by a nonadherent contact layer, an absorbent foam dressing and secured with a gauze wrap. The patient was instructed to properly offload the left foot and was given assistive devices to accommodate this. The patient was instructed to change their foam dressing every 3 days with repeat application of OFM occurring at each weekly clinic visit. After one week post-application the wound size had decreased to 4 x 1cm *(Case 2b)* with complete closure occurring at the three-week visit *(Case 2c)*.

Case 3

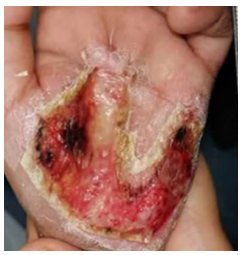
A 4-year-old male with no significant medical history presented after sustaining a severe abrasion injury down to the palmar fascia of the left hand. At the initial visit, the wound measured 4.5 cm x 4cm after initial debridement of non-viable tissue *(Case 3a)*. After debridement, OFM was hydrated with saline and serous wound exudate then applied to the wound bed. A secondary dressing was placed which consisted of a non-adherent contact layer and an absorbent foam dressing which was secured

Case 3. Severe abrasion injury.

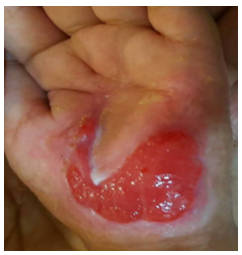
- A 4-year-old male, no significant medical history presented with a severe abrasion injury of the left hand down to the palmar fascia
- On application to the wound bed OFM hydrated with saline and wound exudate and covered with non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap
- The parents were instructed to change their foam dressing every three days or sooner if required. Application of OFM occurring at each weekly clinic visit
- At the 12 week follow up the wound was fully granulated with roughly 30% of the would remaining.



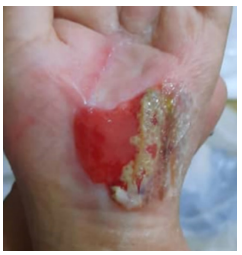
a. Initial defect, measuring 4.5 x 4.0cm, palmar fascia exposed



b. Week 1 follow up, pre-debridement, wound measuring 3.5 x 3.0cm



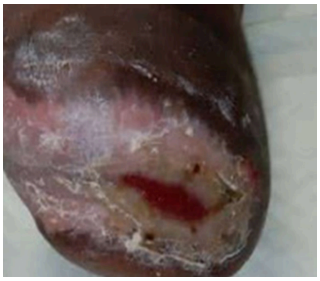
c. Week 10 follow-up, post-debridement, wound measuring 2.5 x 2.5cm



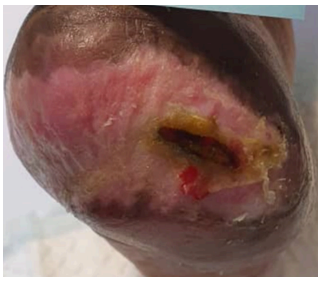
d. Week 12 follow-up, pre-debridement wound measurement 2.3 x 2.5cm

Case 4. Surgical wound dehiscence of a trans-metatarsal amputation two years ago

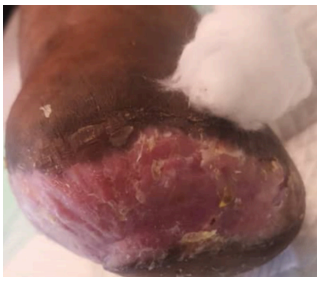
- A 29-year-old male with insulin-dependent diabetes mellitus and hypertension presented to the clinic for evaluation of a non-healing ulcer persisting on the left foot from a surgical wound dehiscence of a trans-metatarsal amputation two years ago
- On application to the wound bed OFM hydrated with saline and wound exudate and covered with non-adherent contact layer, absorbent foam dressing and secured with a gauze wrap
- The patient was instructed to change their foam dressing every three days. Application of OFM occurring at each weekly clinic visit
- Complete closure occured by week two.



a. Initial defect measuring 2.7 cm x 0.7 cm



b. Week 1 follow up, pre-debridement wound measuring 2.0 cm x 0.5 cm



c. Week 3 follow up, defect 100% reepithelialised

by a gauze wrap. The patient's family was instructed to change the foam dressing every three days or sooner if the dressing became soiled or saturated. The patient was seen in the clinic weekly for repeat application of OFM. After one week, the palmar fascia was covered by granulation tissue *(Case 3b)* and at the 10-week follow up the wound size had decreased by over 60% *(Case 3c)*. At the last clinic visit, the wound was fully granulated with reepithelialisation and roughly 30% of the would remaining *(Case 3d)*.

Case 4

A 29-year-old male with past medical history of insulin-dependent diabetes mellitus and hypertension presented to the clinic for evaluation of a non-healing ulcer persisting for two years on the left foot from a surgical dehiscence of a previous trans-metatarsal amputation. At the initial visit, the wound measured 2.7 x 0.7cm after initial debridement of non-viable tissue *(Case 4a)*. After debridement, OFM was hydrated with saline and serous wound exudate and then applied to the wound bed. The wound was dressed with a non-adherent contact layer, secondary foam dressing and secured by a gauze wrap. The patient was instructed to properly offload the left foot and was given assistive devices to accommodate this. The patient was instructed to change their foam dressing every three days with repeat application of OFM occurring at each weekly clinic visit. After one week post-application the wound size had decreased to 2.0 x 0.5 cm *(Case 4b)* with complete closure at week two *(Case 4c)*.

Discussion

Chronic wounds represent a global healthcare burden that requires a multidisciplinary approach to achieve wound closure. What makes chronic wounds such a challenge for clinicians to treat are the complexities of a wound, such as moisture management, the presence of tunnelling/undermining, and/or the presence of biofilm. In addition to these challenges, clinicians also must address the patient's underlying chronic comorbidities. With the global rising rates of obesity (Chooi et al, 2019), diabetes (Lin et al, 2020) and peripheral vascular disease (Fowkes et al, 2017), the number of patients dealing with chronic wounds is also projected to significantly increase (Sen, 2019). There are several compounding factors in addition to comorbidities that make achieving wound closure difficult. For example, it has been documented that developing countries have less access to quality healthcare, an inadequate healthcare structure, lack of universal healthcare and limited access to healthcare resources (Gupta et al, 2021). As the complexity of these wounds increases there is a growing need for advanced modalities to aid wound healing. Currently there are no ECM-based products accessible to Malaysian healthcare providers. Unfortunately, this situation is not isolated to Malaysia as many developing countries struggle with gaining access to these advanced technologies (Serena, 2014). By providing patients with an advanced wound

care technology such as OFM, there is potential to heal wounds quicker and improve their overall quality of life (Kapp and Santamaria, 2017). In our initial evaluation of OFM in a range of complex wounds and comorbidities 90% (9/10) of the wounds were deemed closed or improving at the 12 week follow-up with the remaining patient lost to follow-up.

Although developing countries have had limited access to these advanced ECM-based products, developed countries such as the US have been using OFM for over 10 years. To date OFM has been used in a variety of wounds ranging from chronic lower extremity wounds to acute surgical wounds (Liden and May, 2013; Simcock et al, 2013; Bohn and Gass 2014; Gonzalez 2016; Hughes et al, 2016; Ferreras, et al, 2017; Lullove 2017; Raizman et al. 2020). The patients in this retrospective case series demonstrate a similar mix of wound aetiologies including post-operative surgical dehiscence wounds, DFUs, VLUs and acute traumatic wounds. Despite the complexities involved in this case series, there was a 57% area reduction at 4 weeks. Percentage area reduction is a key indicator of the likelihood of wound closure (Coerper et al, 2009). Given the difficulty in healthcare access, the average age of the wound on presentation, 55 weeks, was significantly higher than may be expected. Wound chronicity presents another challenge for the clinician as there is likely to be a high level of bacterial bioburden and associated biofilm present on presentation (Grice and Segre, 2012). This in conjunction with elevated levels of matrix metalloproteinases (MMP) in the wound bed can lead to significant difficulty in facilitating wound closure (Metcalf and Bowler 2013; Lazaro et al, 2016). This is where an advanced ECM-based product, such as OFM, can help advance the wound out of the chronic inflammatory phase and into the proliferative phase by modulating the imbalance of MMPs and tissue inhibitor of metalloproteinases (Negron et al, 2012) as well as preventing biofilm formation (Karnik et al, 2019).

All wounds included in the case series showed significant changes in granulation tissue and 3/10 wounds closed at 12 weeks. Some of the factors that lead to delayed wound closure were difficulty with patient compliance in returning to the clinc for weekly application of OFM, difficulty with maintaining the agreed upon dressing change plan and patients being lost to follow-up for long periods of time. All these factors can elongate the time to full wound closure. Despite the previously mentioned compliance issues, the benefits of OFM can be seen by the improvement in wound bed appearance in 90% of the wounds after the application of OFM. By providing more patient education, clinician education and improving access to healthcare, one can imagine how these factors would contribute to increasing the percentage of wound closure.

Limitations

As with all retrospective case series, this analysis lacks a control or active comparison, patient and physician blinding and standardisation of procedures. Also, given the difficult access to healthcare on a routine scheduled basis patients were lost to follow-up for periods of time when they were not receiving additional wound care. Additional limitations include a small sample size and uncertainty in previous treatments. On a separate note, patients were not able to provide additional OFM to the wound bed at interim dressing changes outside of the clinic visits. This is contrary to how the dressing is routinely used in other studies where frequent reapplications of OFM have been described to decrease closure times (Bohn et al, 2017).

Conclusions

In this study an ECM bioscaffold sourced from the forestomach of ovine was used by a single wound care clinic providing patients with an advanced healing technology previously not available to this patient population and an additional tool to aid wound closure. This retrospective case series highlights an initial positive experience implementing OFM as part of standard of care and demonstrated positive healing outcomes in complex chronic wounds. The favourable findings demonstrate the need for further study of OFM as an effective and accessible treatment modality for acute and chronic wounds in Malaysia and Southeast Asia. WAS

Declaration of intereted:

SGD and BAB are employees of Aroa Biosurgery Limited (New Zealand). EndoformR was provided by Aroa Biosurgery Limited.

Acknowledgements

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CASE REPORT

Use of Ovine Forestomach Matrix in the Treatment of Facial Thermal Burns

Rami H. Al Mousa, MD[1]; Brandon A. Bosque, DPM[2]; and Shane G. Dowling, PA-C[2]

ABSTRACT

Introduction. Thermal burn injuries are common, devastating medical emergencies that are challenging to manage. Timely and effective treatment is paramount to both short- and long-term patient outcomes. Currently, medical providers and health care facilities worldwide are emphasizing the need for cost-efficient and accessible treatments; such treatments are particularly vital for vulnerable populations with limited access to advanced medical resources. The use of extracellular matrix (ECM) technologies has become widespread in the management of acute and chronic wounds, including burns. Ovine forestomach matrix (OFM) is an ECM bioscaffold isolated from sheep forestomach tissue and has been shown to be effective in soft tissue reconstruction procedures. **Case Report.** The use of OFM in the treatment of 2 facial thermal burn injuries, including in a pediatric patient, is described. Both patients fully recovered from their facial injuries with satisfactory cosmetic outcomes. **Conclusions.** Although OFM technology is widely used in the management of acute and chronic wounds, the authors believe this to be the first published report of its use to aid healing in burns. Ovine forestomach matrix may provide a valuable additional tool for the management of complex burns.

KEYWORDS

wound healing, burns, pediatrics, tissue engineering, biomaterials, ovine forestomach matrix, extracellular matrix, regenerative medicine

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Soft tissue defects secondary to burn injuries can be devastating and difficult to treat. The incidence of facial burns varies by country but has been reported to range between 27% and 60%.[1] These facial burn injuries are often extremely painful and prone to infection, and acceptable cosmetic outcomes are critical for the patient.[2] Even if a burn injury progresses to complete closure, concern remains for the longer-lasting sequelae, such as chronic nerve pain, disfigurement, painful fibrotic scar, loss of function, loss of sensation, and psychosocial implications for the patient.[1,3,4] Although the skin of the face tends to be more vascularized than peripheral anatomy, facial burns pose a treatment challenge for multiple reasons. Skin contracture is common in areas of the face with underlying mobile tissues, whereas the forehead is at increased risk of exposed bone and the associated challenges of achieving adequate coverage.[5] Eyelids and lips are thinner tissues and thus are particularly prone to contracture.[5] Facial burns are also difficult to manage due to airway management, the potential for respiratory compromise resulting from thermal inhalation injury, or postinjury edema.

Ovine forestomach matrix (OFM) is a decellularized extracellular matrix (ECM) bioscaffold that has been used extensively in the management of complex wounds and soft tissue reconstructions, including chronic lower extremity wounds and acute surgical wounds.[6-12] The process of tissue decellularization of the intact ovine tissues removes all cells and cellular debris, leaving an intact, native, and biocompatible scaffold for use in soft tissue regeneration applications.[13] Ovine forestomach matrix contains naturally occurring anti-inflammatory proteins[14] and demonstrates anti-inflammatory properties in vitro and in vivo,[15,16] stimulates blood vessel formation,[17] and is remodeled into functional soft tissue over time.[17,18] The structure of OFM is biomimetic of native soft tissue ECM and serves as a scaffold for fibroblast and keratinocyte migration and proliferation.[13] A proteomic analysis of OFM identified more than 150 known ECM and ECM-associated proteins, including various growth factors (eg, epidermal growth factor, platelet-derived growth factor) and antibacterial proteins, including cathelicidin and β-defensin.[14]

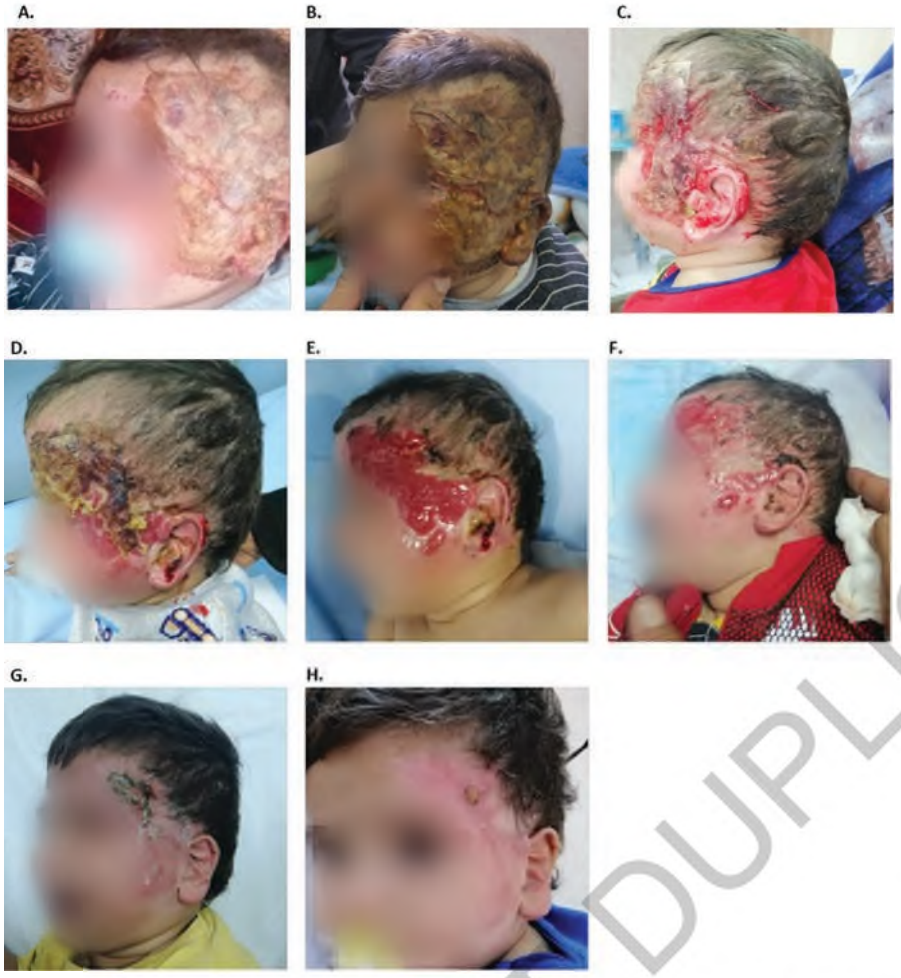

Figure 1. Case 1: A 9-month-old male infant presented with facial burns and was managed with ovine forestomach matrix. (A) At approximately 4 days after initial injury, remote patient evaluation was conducted. (B) At the initial in-person clinical presentation (week 0, approximately 8 days after the initial injury), appearance predebridement showing a covering of more than 80% fibrotic slough (wound dimensions, 13.2×12.7cm). (C) Week 2 (predebridement), showing approximately 75% fibrotic tissue in the wound bed. (D) Week 3 (predebridement), showing 25% granular tissue and 75% fibrotic slough in the wound bed. (E) At week 3 (postdebridement), the wound measured 12.5×10.6cm in size. (F) At week 3.5 (postdebridement), the wound measured 8×6.2cm in size. (G) At week 7, the wound measured 4.3×3.8cm in size. (H) At week 8, the wound was fully epithelialized. Guardian consent was obtained for the publication of the patient's case and photos.

Although the use of OFM in managing chronic wounds has been widely published, few reports describe its use in the treatment of burns. This case report documents the successful use of OFM to treat 2 patients with challenging facial thermal burns. The authors obtained patient or guardian consent to publish the case photos and data.

CASE REPORTS

Case 1

A 9-month-old male infant sustained a thermal burn injury to the entire left side of the face, with portions of full-thickness damage, resulting from an open fire. Because of sociopolitical factors, the patient and family were unable to seek immediate medical attention; thus, the initial evaluation was conducted remotely approximately 4 days postinjury (**Figure 1A**). The patient was evaluated in person approximately 8 days after the initial injury (**Figure 1B**). The skin defect equated to approximately 10% total body surface area (TBSA) for an infant under the age of 1 year. The patient could not be admitted for surgical debridement under anesthesia because of sociopolitical factors.

The initial wound, which measured approximately 13.2 cm × 12.7 cm, presented with a covering of fibrotic slough (>80%), inflammation, and significant drainage, and it was suspicious for infection (**Figure 1B**). Hair follicles adjacent to the left side of the face had been entirely lost, and the patient was experiencing significant discomfort.

The patient had no known comorbidities or other underlying health conditions at the time of treatment. During the initial evaluation, he was treated for a suspected local infection with antibiotic therapy and underwent mechanical debridement of nonviable tissue to the limits of his pain tolerance. Postdebridement (not shown), treatment was initiated with 2 layers of OFM plus 0.3% ionic silver (Endoform Antimicrobial; Aroa Biosurgery Limited) for suspected local infection. After the initial 2-layered OFM application, an additional layer of OFM was applied weekly for 7 weeks. The OFM bioscaffold integrates into the regenerating tissue over time; thus, there is no need to remove the dressing from the wound bed.

Physical examination 2 weeks after the initial in-person consultation revealed resolving soft tissue inflammation, no further clinical signs of infection, and a reduction in nonviable tissue in the wound bed to approximately 75% (**Figure 1C**). By week 3, the patient's discomfort had dramatically reduced (pain score, 0 of 10). This allowed the clinician to perform more aggressive debridement (**Figure 1D**), which revealed a well-granulated wound bed (**Figure 1E**). At 3.5 weeks, approximately 40% of the original skin defect had epithelialized (wound dimensions, 8 cm × 6.2 cm) (**Figure 1F**), and by week 7, the original skin defect had decreased to 4.3 cm × 3.8 cm in size (**Figure 1G**). At week 8, the burn was fully epithelialized (**Figure 1H**), and approximately 10% skin contracture was noted. The neoepithelialized skin was pliable, elastic, and grossly comparable to the patient's normal skin

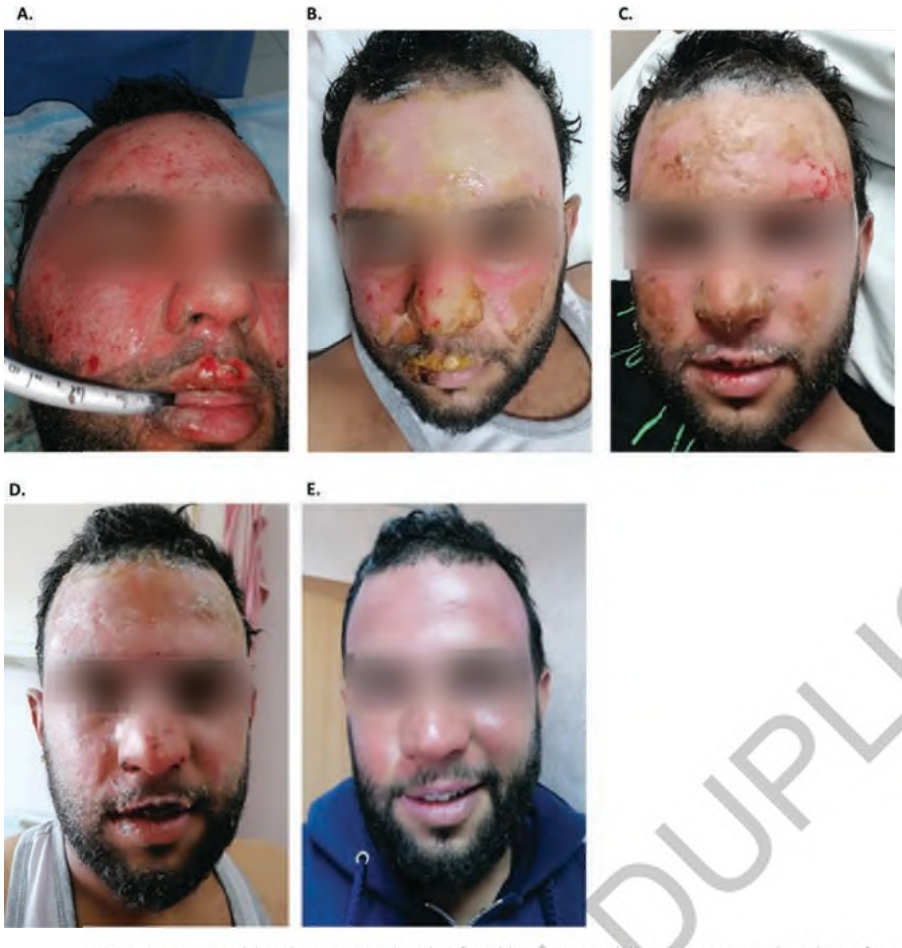

Figure 2. Case 2: A 38-year-old male presented with a facial burn injury. (A) At approximately 2 days after initial injury (postdebridement), the patient initially presented. (B) Four days after initial evaluation (predebridement), showing more than 10%–20% fibronecrotic covering the injury (wound area, 27.9×15.2cm). (C) At 6 days after initial presentation (predebridement), showing minimal desiccated slough. (D) Week 2, after completion of treatment with ovine forestomach matrix. (E) Week 3 follow-up, showing 100% epithelialization. Patient consent was obtained for the publication of the case and photos.

pigmentation. Of note, the hair follicles that had been damaged by the thermal burn had begun to show signs of viability and formation of new hair. The patient had no residual pain, maintained sensation of the damaged area of his face, and resumed normal activities.

Case 2

A 38-year-old male with no significant past medical history sustained a partial-thickness thermal burn injury to most of the forehead and both cheeks secondary to a gas explosion. Initial evaluation was conducted remotely, followed by an in-person examination approximately 2 days postinjury. The skin defect covered approximately 4.5% TBSA. Initially, the wound measured approximately 27.9 cm × 15.2 cm; presented with a covering of fibrotic slough (>50%–60%), inflammation, and notable drainage; and was suspicious for infection. As a result, the patient was admitted to the hospital and an initial debridement was performed (**Figure 2A**). The patient was experiencing significant discomfort, with a pain score of 8 on a 10-point scale. Two days later (4 days postinjury), approximately 10% to 20% of the patient's face was covered by devitalized tissue (**Figure 2B**). After sharp debridement was performed, OFM (Endoform Natural; Aroa Biosurgery Limited) was placed over the injury site, in addition to a layer of hydrogel and secondary gauze dressing. Wound dressings were changed every 48 hours. By 6 days postinjury, the patient's pain score had decreased to 3. Light mechanical debridement was performed to manage a small amount of slough (**Figure 2C**); this was followed by a repeat application of OFM and hydrogel with gauze secondary dressing. At 9 days postinjury, the patient was reevaluated before discharge. The wound area had decreased to 2 cm × 7 cm in size (**Figure 2D**), and wound management transitioned to the application of 2.5% hyaluronic acid cream and sun protection factor 15 sunscreen 3 times daily. By the final follow-up visit, 20 days postinjury, complete epithelialization of the skin had occurred. The neoepithelialized skin was pliable, elastic, and grossly comparable to the patient's normal skin pigmentation (**Figure 2E**).

DISCUSSION

The use of ECM bioscaffold technologies in the management of burn injuries has become widespread.[19] These products are used either as part of a 2-stage reconstructive procedure to build granulation tissue before definitive closure with a split-thickness skin graft (STSG) or in instances in which STSG is not available or is inappropriate. These same technologies can be used to aid closure via secondary intention.[20] Even with the growing clinical evidence to support widespread adoption of ECM technology for advanced burn and wound care, its use may be limited by lack of availability, mostly because of the cost of such treatment.[21]

Extracellular matrix technologies differ significantly from synthetic and semisynthetic bioscaffolds because ECM technologies include naturally occurring ECM proteins that have important biologic roles in soft tissue regeneration following burn injury.[22] As in all wounds, soft tissue regeneration following burn injury typically proceeds via the orderly phases of wound healing, with the inflammatory phase initiated after the initial injury and hemostasis.[23] A prolonged inflammatory phase in

burn healing can lead to hypertrophic scarring, exacerbation of pain, and overall impaired healing.[24] Biologically active molecules present in OFM are known to have anti-inflammatory properties.[25] For example, tissue inhibitors of metalloproteinases (eg, TIMP-4) and serpins are naturally occurring protease inhibitors and are present in OFM.[25] This finding may explain the broad-spectrum inhibitory effect of OFM on matrix metalloproteinases, which are a known contributor to wound chronicity.[15] Ovine forestomach matrix has a native matrix structure composed of proteins to aid cell repopulation, migration, and proliferation[17]; promote angiogenesis[17]; and recruit mesenchymal stromal cells (MSCs).[25] In thermal burn injuries, MSCs have been shown to play a substantial role in regeneration by accelerating epithelialization,[26] differentiating and regenerating the stratified epidermis,[27] and modulating inflammation.[28]

Although many ECM technologies have been commercialized for soft tissue repair, OFM is a commercially available product for which the barriers to access, namely cost, have been significantly reduced.[12] Both patients in this case series had limited access to advanced burn care technologies due to sociopolitical factors, including refugee status. Data from the World Health Organization suggest that more than 95% of burn deaths occur in low- to middle-income countries.[29] Burns are among the most common and devastating medical conditions encountered in refugee camps.[30] Therefore, access to cost-effective advanced ECM technology for the early treatment of thermal burns can have a significant effect on patient outcomes. In a multicenter study, Pham et al[31] found burns that epithelialized in less than 21 days to be at much lower risk of hypertrophic scarring compared with slower-to-heal burn injuries. Shortening the time to wound closure and minimizing contractures can facilitate earlier return to work[32,33] and improve the long-term psychosocial status of survivors of burn injury.[34]

The application of OFM in the patients with significant facial burns in this case report helped to provide immediate coverage and facilitate epithelialization in 20 days (partial-thickness burn) and 56 days (deep partial-thickness burn). Both patients experienced a notable reduction in pain and discomfort. These initial positive outcomes using OFM in the management of challenging partial-thickness and deep partial-thickness facial burns and the accessibility of the products have prompted the authors of this case report to adopt OFM as part of the standard of care for patients with burns. Although no large-scale prospective efficacy studies of OFM in the management of burns have been conducted, the authors' experiences of managing burns reflect outcomes of previously published studies in acute and chronic wounds treated with OFM.

LIMITATIONS

This case report is limited by the sociopolitical factors that may have prevented the current standard of care treatment of acute facial burns. Although the details and management of facial burns vary from patient to patient, to the knowledge of the authors of this case report, this article is the first publication in which OFM was used in the management of burn wounds. Additional studies with larger sample sizes are needed to substantiate the outcomes of the 2 cases reported herein.

CONCLUSIONS

Thermal burns are painful soft tissue defects that are challenging to manage. Such injuries can benefit from the use of advanced technologies to accelerate wound closure and reduce the risk of complications. This case report suggests that OFM is a cost-effective treatment for partial-thickness and deep partial-thickness facial thermal burns that provides immediate coverage, builds granulation tissue, and aids epithelialization at the site of burn injury.

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Extracellular Matrix–Based Collagen Dressings for Scalp Repair Following Mohs Micrographic Surgery

Igor Melnychuk, MD; Inna Servetnyk, MD; Noah Kosnik, DO

PRACTICE **POINTS**

- Patients who undergo Mohs micrographic surgery on the scalp are prone to developing complications such as infection, wound dehiscence, and partial or full-thickness skin graft necrosis.
- Use of extracellular matrix–based dressings may assist with deep wound healing on the scalp.

To the Editor:

Squamous cell carcinoma (SCC) is the second most common cancer of the scalp.[1] Mohs micrographic surgery is used to treat SCC, and it commonly generates a 2.5×2.5-cm open wound with exposed bone.[2] Although Mohs micrographic surgery effectively treats cutaneous lesions, it carries a high risk for complications such as infection, wound dehiscence, and partial or full-thickness skin graft necrosis.[3] Recommended therapies to decrease these complications include linear closures, flaps, and peripheral autograft tissue.[4] However, these procedures do not come without risks and carry their own complications. Therefore, we suggest a safe, less-invasive initial approach using a synthetic extracellular matrix (ECM)–based collagen dressing for secondary wound closure.

A 76-year-old woman presented to the infectious disease clinic at Monument Health Rapid City Clinic (Rapid City, South Dakota) for evaluation of a dehisced scalp wound 3 months following Mohs micrographic surgery for scalp SCC. The wound underwent primary closure

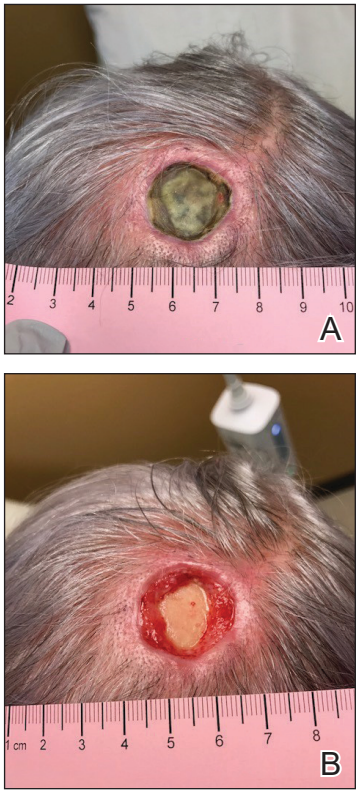

FIGURE 1. A, Initial presentation of a chronic wound with dehiscence on the scalp following Mohs micrographic surgery. B, The wound was debrided.

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The authors report no conflict of interest.

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following surgery and dehisced shortly after (Figure 1A). Various oral antimicrobials were used by the dermatologist to assist with wound closure but without success. The patient was referred to the wound clinic for management. At the first appointment, all necrotic tissue was debrided and the cranium was exposed in the wound base (Figure 1B). The wound measured 2.3×2.3×0.2 cm. An ECM-containing collagen dressing (Endoform Natural Restorative Bioscaffold [Aroa Biosurgery Inc]) was used to provide a scaffold for wound closure (Figure 2A). It was dressed with the petroleum-based gauze Xeroform (Cardinal Health) and covered with dry gauze to prevent evaporation and provide moist wound healing. The wound developed some budding tissue islands 3 weeks after weekly ECM-based collagen dressing applications (Figure 3A). The wound continued to decrease in size and formed an isthmus by the second month of therapy (Figure 3B). The wound fully closed within 3 months and showed minimal scarring after 3 years (Figure 2B).

Chronic wounds usually get trapped in the inflammatory stage of wound healing due to destruction of growth factors and ECM by metalloproteases (MMPs), which creates a vicious cycle and wound stalling. Wound debridement converts a chronic wound back into an acute wound, which is the first step of healing. Following wound debridement, collagen-based dressings can assist with healing by binding the destructive MMPs, and ECM matrix promotes the building of new tissue. The 3 most commonly used ECM-based collagen dressings are Endoform, PuraPly AM (Organogenesis Inc), and Puracol Ultra ECM (Medline Industries, Inc).

Endoform is ovine-based collagen and provides a natural porous bioscaffold for rapid cell infiltration.[5] It contains more than 150 ECM proteins along with residual vascular channels that help re-establish new vasculature. Ovine-based collagen contains collagen types I, III, and IV arranged as native fibers that retain the 3-dimensional architecture present in tissue ECM.[5] Although MMPs are essential in normal healing, the elevated presence of MMPs has been linked to stalled wound healing. Clinical observation and assessment may not be sufficient to identify a wound with elevated protease activity that can break

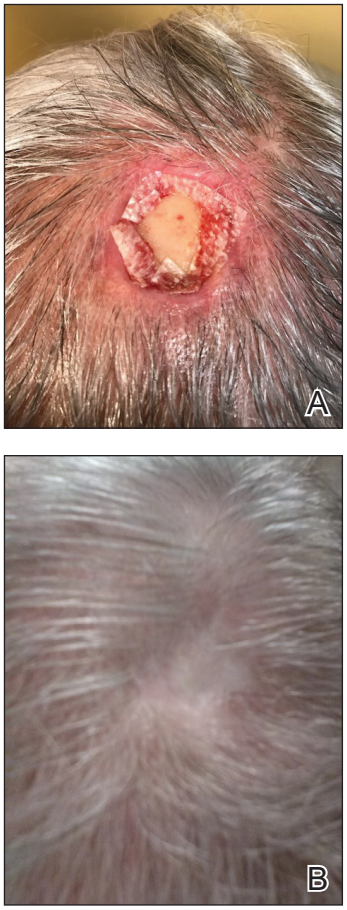

FIGURE 2. A, An extracellular matrix–based collagen dressing (Endoform Natural Restorative Bioscaffold [Aroa Biosurgery Inc]) was applied to the wound. B, The wound showed minimal scarring 3 years after closure.

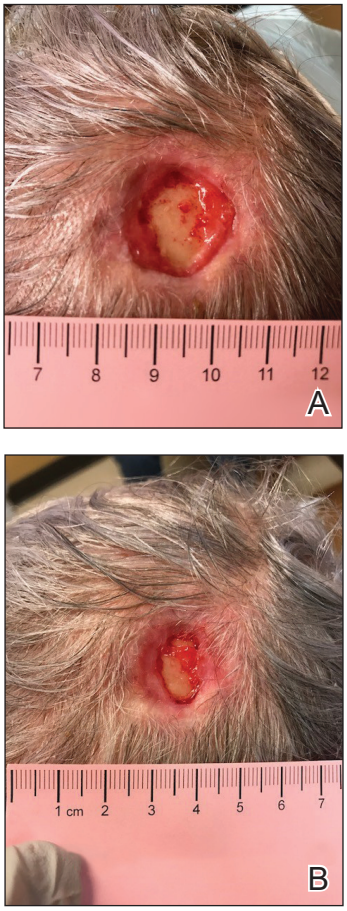

FIGURE 3. A, Budding tissue islands developed on a scalp wound 3 weeks after application of an extracellular matrix–based collagen dressing (Endoform Natural Restorative Bioscaffold [Aroa Biosurgery Inc]). B, An isthmus developed 7 weeks after application of Endoform.

down ECM, affect wound fibroblasts, and impair growth factor response. Although collagen ECM itself does not contain any growth factors, it preserves the destruction of native ECM and growth factors by MMPs by functioning as a sacrificial substrate. The addition of 0.3% ionic silver to the ECM has been shown to decrease bacterial growth and prevent biofilm formation.[6]

PuraPly AM is a native, type I porcine collagen matrix embedded with the polyhexamethylene biguanide for the management of chronic wounds.[7] The addition of polyhexamethylene biguanide to the ECM matrix provides bactericidal activity against biofilm formation.[8] PuraPly AM reduced the counts of biofilm-producing pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Candida* species, and *Aspergillus niger* in nonclinical studies. Use of polyhexamethylene biguanide has been seen within ECM grafts (PuraPly AM).

Puracol Ultra ECM is made of porcine mesothelium and is comprised of types I, III, and IV collagens; elastin; fibronectin; laminin; and proteoglycans. It also contains fibroblast growth factors, contributing to angiogenesis in the wound.[9]

Application of ECM-based collagen dressings on debrided wounds requires moisture for absorption. Because cranium wounds lack sufficient exudate production, dermal templates need to be hydrated with sterile normal saline before application and covered with a moisture-retaining dressing. Extracellular matrix–based dressings are biodegradable and can be reapplied every 5 to 7 days. For chronic wounds, application of collagen dressings, such as Endoform, is essential and could be considered as the first step prior to switching to more advanced wound care modalities.[6,10] Additional studies investigating ECM-containing may determine their comparative efficacy.

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WOUNDS ® Key Concepts in Healing Venous Leg Ulcers

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Key Concepts in Healing Venous Leg Ulcers

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ABSTRACT: VLUs represent 90% of lower extremity ulcers. They affect 1% of the general population and 2.2% of the Medicare population. That same incidence is seen in Europe where 1% of the population is affected. The incidence is 4 times as high in underdeveloped countries. Recent discoveries have helped better define the chronic nature of venous ulcer pathophysiology. Applying recently developed key concepts in a venous ulcer treatment plan may bring about improved healing outcomes. Important clinical considerations include the effective management of biofilm, control of protease levels, and the role of high-density ECM collagen in healing. For the practitioner, having a better understanding of pathophysiology and using a goal-directed treatment plan can be helpful in delivering quality outcomes for patients with VLUs. With the goal of improving outcomes for this patient population, this article provides awareness of key concepts directed at a modern pathophysiological approach for managing VLUs.

Introduction

VLUs are the most common ulcer of the lower extremity, representing nearly 90% of lower leg ulcers.[1,2] Prevalence of VLUs in the US population is 1%; when considering patients with ulcers and healed ulcers, this percentage increases to 1.8%.[1,2] In the United States, approximately 0.5% of patients who are privately insured have been reported to have VLUs, whereas the prevalence of VLUs in the Medicare population has been reported to be 2.2%.[2] There are over 6 million patients with VLUs in the United States.[3] In terms of cost, management of VLUs costs an estimated $14.9 to $17.4 billion dollars annually in the United States.[2,4] The reported average cost per patient of $5527 is anticipated to increase.[4]

In western Europe, the incidence of VLUs is similar to that of the United States at 1% of the population. Global estimation may be harder to compare, but data indicate a higher incidence in developing countries. Incidence rates of 4.5 per 1000 patient-years in India, 3.5 per 1000 patient-years in China, and 1.7 per 1000 patient-years in Brazil have been reported.[5]

In addition to the cost of treatment, patients with VLUs experience the economic loss of time off work and low quality of life scores.[2,6,7] Healing rates are often poor for VLUs. Healing can be protracted, with fewer than 60% healed by 12 weeks, and recurrence rates are high, with nearly 75% recurring within as little as 3 weeks.[8] Rates of venous ulceration tend to be higher and more commonly associated with older age, concomitant chronic venous insufficiency, female sex, obesity, a history of DVT or phlebitis, immobility, or a congenital absence of veins.[1,7,8]

Patients with VLUs will represent a significant portion of any wound care practice. For the practitioner, having a better understanding of pathophysiology and using a goal-directed treatment plan can be helpful in delivering quality outcomes for this population of patients. Awareness of key concepts directed at a modern pathophysiological approach can bring about improved outcomes for patients.

Keywords: etiology, matrix metalloproteinase, peripheral arterial disease, venous leg ulcer

Abbreviations: DVT, deep vein thrombosis; ECM, extracellular matrix; MMP, matrix metalloproteinase; ORC, oxidized regenerated cellulose; PAD, peripheral arterial disease; VLU, venous leg ulcer.

Etiology

Macro disease occurs in the dependent venous system in the legs. Whether the disease is congenital in origin or acquired after DVT, valvular incompetence results in further vein dilatation and thus further valve incompetence results. Commonly seen in the superficial saphenous system, venous hypertension can be transmitted to the deep system through the connecting perforator vessels. The calf muscle pump fails to move blood from the lower leg, and the result is venous hypertension. Venous hypertension can be demonstrated in greater than 84% of patients with ulceration.[9] The resultant venous hypertension in turn affects the microcirculation. It is at the microcirculation level that more molecular-based tissue damage and chronicity in this disease state are observed.[3,9] Dermal changes are seen, such as hemosiderin hyperpigmentation, lipodermatosclerosis, and ulceration of the skin.[3,9] The resultant microangiopathy with elongation and dilatation of the capillary beds leads to cyclical changes of capillary endothelial damage, widening of the interendothelial space, capillary cuffing, and pericapillary edema that increase vascular permeability and lead to accumulation of extravasated fluid. Leukocytes accumulate as do inflammatory macromolecules, leading to tissue damage and perpetuating ulceration.[3,9] The surrounding tissue is damaged by activation of increased amounts of cytokines, chemokines, MMPs, iron-free radicals, upregulated oxygen radicals, and nitrogen radical species.[3,9] The proinflammatory nature of venous ulceration should be carefully considered when treating these chronic wounds. Likewise, an understanding of how treatment will affect the proinflammatory nature of the wound should lead to improved healing. Treatment strategies addressing both the proinflammatory nature of the ulcer as well as improving the microcirculatory changes (ie, local tissue edema and extravasation) should be effective.

Pathophysiology of Venous Ulcers

VLUs are characterized and perpetuated by their inflammatory characteristics. While the process of venous hypertension leads to leaking capillaries and the release of inflammatory mediators and leukocytes, failure to heal and the presence of an open wound also leads to bacterial consequences. The concept of critical colonization has been replaced by the recognition that bacterial biofilms develop on the wound surface.[10] The constant presence of bacteria causes a chronic state of inflammation as the immune system reacts to but cannot clear the bacteria organized into a biofilm.[10] A recent meta-analysis identified that 78.2% of hard-to-heal wounds have biofilm whereas only 6% of acute wounds have biofilm.[11] The presence of biofilm produces MMPs as leukocytes respond to the presence of bacteria. That influx of inflammatory cells leads to an excess of protease activity that degrades tissue and prevents healing. Bacteria in and of themselves produce protease, which can be an indicator of virulence and likelihood of infection.[12]

Visual inspection and surface culture do not accurately identify bacterial biofilm nor estimate virulence and infectivity.[12] Therefore, using a validated point-of-care device to assess for invasion by common pathogenic bacteria would seem appropriate.[12,13] Identifying pathogenic bacteria can direct therapy so as to avoid infection and decrease the impact those bacteria have in attracting leukocytes that lead to protease excess. Additionally, bacterial proteases do participate in the breakdown of essential proteins and the ECM.[12,14] Protease activity supports the development and accumulation of biofilm while attracting leukocytes to the wound, elevating the MMP levels responsible for ECM destruction.[15] While there are no published data on wound-derived bacteria and the formation of biofilm, biofilm-forming bacteria have been shown to be more productive in developing biofilm in alkaline environments.[16]

The effect of MMPs on healing cannot be understated. When present in excess, leukocyte-produced MMPs delay or prevent wound healing. In one analysis, detection of an elevated MMP level by point-of-care testing was associated with impaired or failed healing of 90% of wounds.[14] Wounds that fail to heal will continue to fail as long as MMP levels are elevated.[14,15,17] To move wounds toward healing and closure, employing strategies to reduce MMP levels would seem effective.

Examinations of wounds treated with high-density ECM collagen (Endoform Collagen Dressing; Aroa BioSurgical) have demonstrated that MMP levels decrease over time. Comparisons of MMP levels with wound area have demonstrated that reducing MMPs brings about a correlating reduction in wound size (**Figure 1**).[18] The reduction in wound size lags behind MMP reduction by approximately 2 weeks. When MMP levels increase (**Figure 2**), the wound enlarges as healing stalls.[18] Elevated MMP levels break down the ECM as it is produced to heal the wound. Architecturally, the ECM provides the structure with which fibroblasts interact in signaling the next-step processes that then differentiate to other tissue functions.[10] Integrins in the ECM are central to this process. Healing is a dynamic process that relies on cellular signaling and reciprocal interactions between cells and the ECM.[10] As the cell attaches to the ECM via integrins, integrin signaling and resultant structural support work to direct gene expression, protein synthesis, actin organization, cell polarity, differentiation, proliferation, and cellular migration.[10] Cytoskeletal distortions cause changes that lead to differentiation. Without that structure, healing processes stall, and chronicity ensues.

Elevated MMP levels break down and degrade the collagen that structurally defines the ECM. Multiple MMPs can participate in degradation and result in a damaged ECM. Primary MMPs involved in the process are the collagenases MMP-1 and MMP-8 and the gelatinases MMP-2 and

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MMP-9.[18] Within structurally intact ECM, collagen degradation can be conceptualized as a stepwise process. MMP-1 and MMP-8, the collagenases, make the first cut in intact collagen by exposing collagen.[19] The collagenases unwind the triple helical structure of the collagen, exposing it to degradation into smaller pieces (peptide segments). MMP-2 and MMP-9, the gelatinases, then come in and degrade the exposed collagen into smaller and smaller peptide pieces.[19] Neutrophil elastase is also present in inflammatory wounds and is a potent serine proteinase that degrades tissue.[18]

Of note, MMP activity is pH senstive. Protease activity is increased in alkaline environments and reduced by acidic lower pH.[16] Consequently, the alkaline pH of hard-to-heal wounds may well promote protease activity.[16]

Goal-directed Treatment

Treatment planning starts with assessment of the patient and using data to predict response to treatment. Having a secure diagnosis is key to proceeding with confidence in the effectiveness of the proposed therapy. Venous duplex imaging of the veins and valves for confirmation of venous disease is the most common imaging confirmatory study and should be part of the initial evaluation. With a confirmed diagnosis, ulcer healing within 12 weeks should be the goal in treatment planning.

Using Margolis-Kantor data to assess patients at presentation can help frame the treatment plan and process (**Figure 3**).[16,20] According to a multicenter study from 2000, Margolis and Kantor found that VLUs with areas of less than 10 cm^2 that were present for less than 12 months in patients who did not have PAD had an 81% chance of healing by 24 weeks.[20] Conversely, ulcers with areas measuring greater than 10 cm^2, those present for 12 months or more, or those in patients with PAD had only a 22% chance of healing at 24 weeks.[20,21] The implication is that larger ulcers and those in patients with long-standing disease or concomitant PAD will be harder to heal. The response to treatment in the first 4 weeks, measured as a reduction in wound area, has been shown to be most relevant when predicting the likelihood to heal. Those wounds that responded to therapy and demonstrated a reduction in wound area by 30% or more were more likely to heal by 12 weeks.[20,22-24]

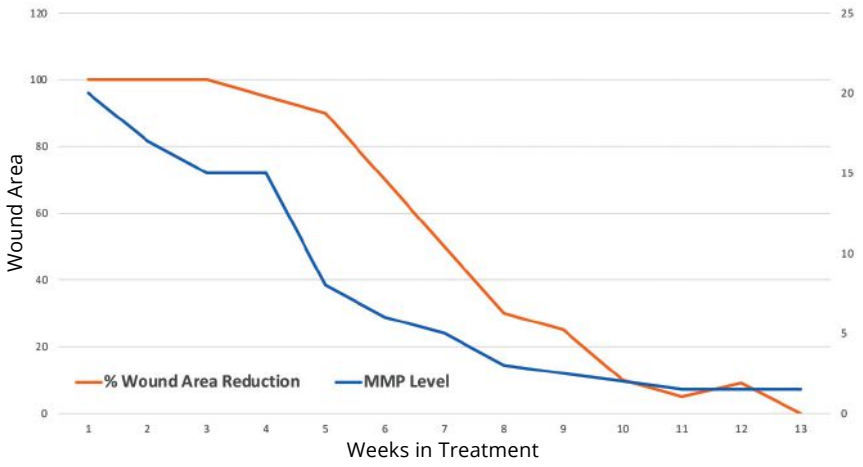


Figure 1. Wound size decreases follow as MMP levels fall.[18]
Abbreviation: MMP, matrix metalloproteinase.

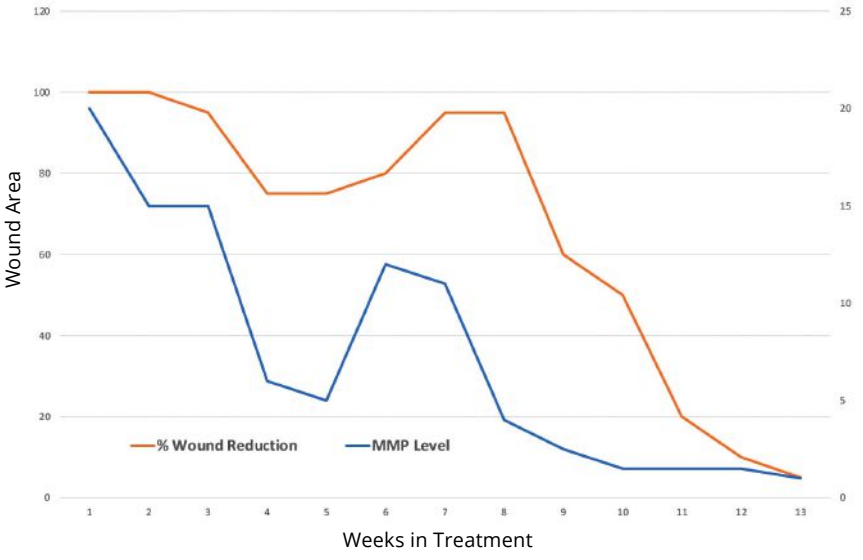
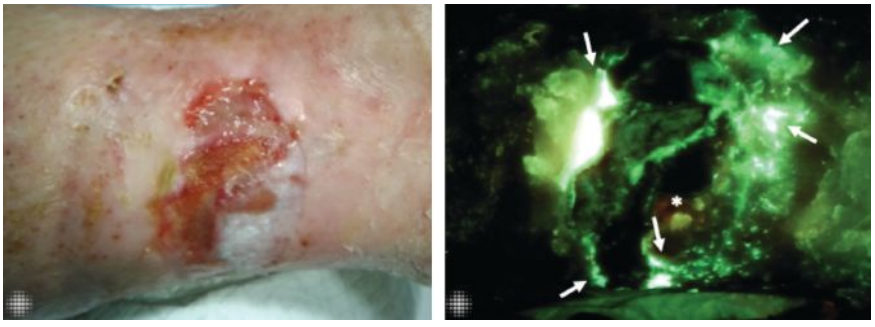


Figure 2. Wound healing stalls while MMP levels rise.[18]
Abbreviation: MMP, matrix metalloproteinase.

The need for treatment directed at both macrovascular and microvascular changes seems apparent given the current understanding of both venous hypertension in the saphenous vein system and the destructive environment created in the wound by biofilm and elevated MMP activity. While compression therapy will be addressed in greater detail later in this compendium, it is important to note the effect that compression has on the wound microenvironment. Not only does compression therapy address the edema caused by venous hypertension, but it also can lower the levels of MMPs and produce a dramatic effect on healing. Beidler et al reported on compression therapy and its effect on harmful MMP levels.[25] Results from their study confirmed the reduction

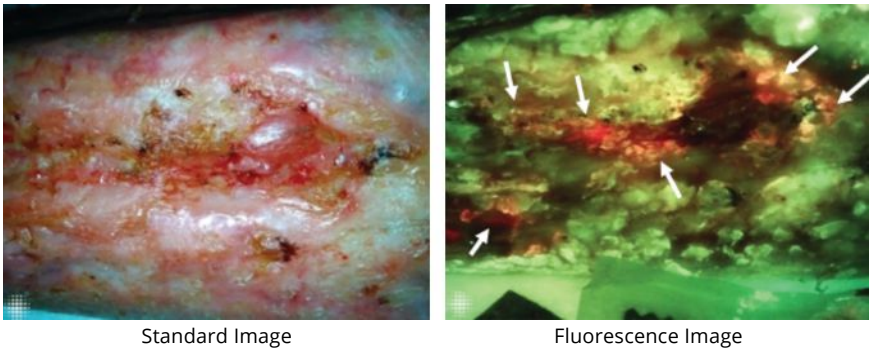
Positive Prognostic Factors	Negative Prognostic Factors
VLU: <10cm^2	**VLU:** ≥10cm^2
Duration: <12 mos	**Duration:** ≥12 mos
Absence of PAD: ABI >0.80	**Absence of PAD:** ABI <0.80
Closure from baseline at 4 wk: ≥30%	**Closure from baseline at 4 wk:** ≤30%

Figure 3. Predictors of healing for VLUs.
Abbreviations: ABI, ankle-brachial index; mos, month(s); PAD, peripheral arterial disease; VLU, venous leg ulcer; wk, week(s).



Standard Image Fluorescence Image

Figure 4. The cyan color (white arrows) on fluorescence imaging of this venous leg ulcer indicates the presence of *Pseudomonas* at the wound edge and in the periwound region. Red fluorescence is also present in the wound bed (asterisk), indicating presence of other bacterial species.



Standard Image Fluorescence Image

Figure 5. The presence of red fluorescence (white arrows) on fluorescence imaging of this venous leg ulcer indicates locations with bacterial loads above 10^4 CFU/g.
Abbreviation: CFU, colony-forming unit.

in MMP-1, -2, -3, -8, and -9 with adequate compression. All 5 MMPs are implicated in delayed wound healing when present in excess amounts.[25] As a result of lowering MMP levels, higher rates of wound healing were identified at 4 weeks.[25] Based on the reduction in MMP activity level, Beidler et al were able to identify good healers, average healers, and poor healers.[25]

Having an effective biofilm strategy is important in healing VLUs. While there are many topical treatments that can be applied to limit reformation of a biofilm, antibiotics are to be used only when invasive infection is present. Elevation in bacterial protease can also help identify infection risk.[12] The commonly used practice of debridement has been shown to improve wound healing.[26-28] While the role of debridement has been studied, recent focus has been on the role of debridement in managing biofilm. The use of bacterial autofluorescence imaging (MolecuLight i:X; MolecuLight Inc) during debridement has improved healing outcomes by identifying more complete removal of biofilm and bacteria (**Figures 4, 5**). Use of autofluorescence imaging to guide debridement has been shown to be helpful in more completely removing the bacterial load from the wound surface. In one randomized, controlled trial, the 12-week healing rates doubled from 22% in the standard of care group to 45% in the group that underwent autofluorescent-guided debridement.[29]

When applied appropriately to a hard-to-heal wound, collagen is an effective modulator of excess MMP activity, reversing the destructive effects of MMPs and thereby initiating wound healing (**Figure 1**). Broad-spectrum MMP buffering has been demonstrated with ECM collagen dressings. In multiple tests, ORC collagen dressings (Promogran Matrix; 3M) affected a more narrow spectrum of MMPs.[18,30] In vitro testing of ECM collagen dressings confirmed potent reduction in collagenases (MMP-1 and MMP-8), gelatinases (MMP-2 and MMP-9), and stromelysin (MMP-3).[18] ORC collagen had activity to lower the gelatinases (MMP-2 and MMP-9) while the collagenases and panel of proteases remained relatively unaffected.[18,30] Once MMP activity is lowered to a certain level, the wound progresses toward a healing trajectory for closure (**Figure 1**).[18,30] If MMP activity increases, a typical wound could experience stalled healing or enlarge (**Figure 2**).[18]

In addition, ECM collagen provides a provisional ECM that stimulates healing. Recent research has demonstrated that the remodeling of the provisional matrix releases a stem cell chemotactic factor, the May-Day protein. Macrophage-induced cleavage of decorin, via MMP-12, releases the chemotactic molecule May-Day, which in turn recruits cells to the site of damaged tissue.[31] The healing benefit of attracting stem cells to the wound site seems intuitive; however, further study will help clarify and define that benefit. Collagen fibril density has been demonstrated in vitro to impact differentiation of wound macrophages,

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converting them to resident macrophages and supporting fibroblast differentiation.[32] ECM collagen dressings have intact collagen and high fibril density. Compared with ORC collagen in treating VLUs, ECM collagen dressings have been reported to enhance and expedite healing (**Figure 6**).[33]

In a study conducted in a US Veterans Affairs hospital, early treatment of ulcers with ECM collagen resulted in improved wound healing outcomes. Using ECM collagen brought about a significantly greater number of wound closures while decreasing the number of advanced cellular or tissue-based products used.[5] The impact of utilizing key concepts in a goal-directed treatment plan can be illustrated in **Figure 7**. While Margolis-Kantor data would suggest this large VLU would be difficult to heal, biofilm management and MMP buffering were employed in combination with effective compression to elicit efficient healing.

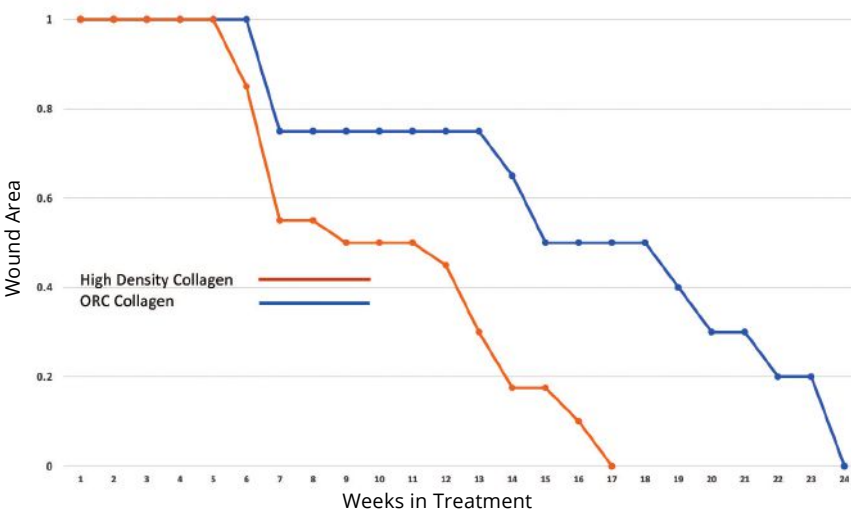

Figure 6. High-density extracellular matrix collagen heals ulcers in a shorter period of time. Abbreviation: ORC, oxidized regenerated cellulose.

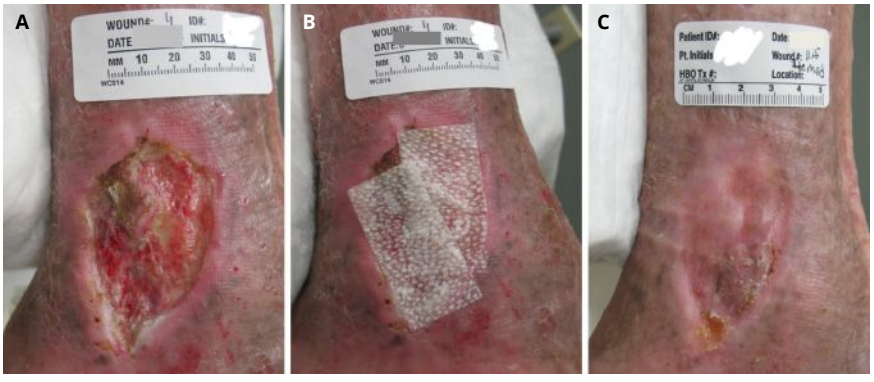

Figure 7. Venous leg ulcer present for more than 22 months that failed multiple advanced modality therapies; (A) on presentation, dimensions were 3.7 cm × 6.3 cm, and area was 23.31 cm^2. Large size and duration are negative predictive indicators for healing and have been associated with a 22% or less chance of healing by 24 weeks. (B) Application of high-density ECM collagen dressings. (C) Wound healed by 20 weeks with compression, attention to biofilm, and high-density ECM collagen dressings. Abbreviation: ECM, extracellular matrix.

Conclusion

The pathophysiology of VLUs has been more completely elucidated in recent years. Compression therapy has been used to treat the resultant edema and, in addition, demonstrated to lower MMP levels in this inflammatory, highly proteolytic ulcer.[25] The role of biofilm in causing inflammation in hard-to-heal wounds suggests the importance of dispersing this microbiome to foster improved healing. Elevated MMPs in a hard-to-heal VLU can be modulated and lowered by applying collagen to the wound. High-density collagen dressings with a broad spectrum of activity and intact collagen may be even more effective for balancing MMP levels and correcting the destruction of ECM. ECM restoration by supplying a provisional matrix can restart the repair process. An effective biofilm management strategy and MMP-modulating therapy may result in improved healing outcomes. Implementing these key concepts in conjunction with adequate leg compression, fluorescence-guided debridement, and early use of ECM high-density collagen dressings as a part of a goal-directed treatment plan may well improve healing outcomes, shorten time to heal, and reduce costs overall.

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