AROA

Myriad™

Plastics and Reconstructive Surgery

Simcock, J., & May, B. C. (2013). Ovine forestomach matrix as a substrate for single-stage split-thickness graft reconstruction. Eplasty, 13, e58.

Chaffin, A. E. and M. C. Buckley (2020). “Extracellular matrix graft for the surgical management of Hurley stage III hidradenitis suppurativa: a pilot case series.” J Wound Care 29(11): 624-630.

Bohn, G. A. and A. E. Chaffin (2020). “Extracellular matrix graft for reconstruction over exposed structures: a pilot case series.” J Wound Care 29(12): 742-749.

Bohn, G. A. (2020). “Using Ovine Extracellular Matrix in Difficult to Close Excisions of Common Skin Cancer: an Evolving New Technique.” Surg Technol Int 37: 49-53.

Desvigne, M. N., K. Bauer, K. Holifield, K. Day, D. Gilmore and A. L. Wardman (2020). “Case Report: Surgical Closure of Chronic Soft Tissue Defects Using Extracellular Matrix Graft Augmented Tissue Flaps.” Frontiers in Surgery 7(173).

Chaffin, A. E., S. G. Dowling, M. S. Kosyk and B. A. Bosque (2021). "Surgical reconstruction of pilonidal sinus disease with concomitant extracellular matrix graft placement: a case series." J Wound Care 30(Sup7): S28-S34.

Hamaguchi, R., T. L. Wearda, A. S. Volk, K. M. Kramer, A. B. Kimball, A. E. Chaffin and D. P. Orgill (2022). "Surgical Management of Hidradenitis Suppurativa: A Two-Center Retrospective Study." Plast Reconstr Surg 150(5): 1115-1127.

Hsu, A., K. Schlidt, C. R. D’Adamo, B. A. Bosque, S. G. Dowling and J. H. Wolf (2023). "Surgical management of perianal fistula using an ovine forestomach matrix implant." Techniques in Coloproctology.

Awad, S. S., J. D. Stern, C. T. Milne, S. G. Dowling, R. Sotomayor, E. A. Ayello, L. J. Feo Aguirre, B. Z. Khalaf, L. J. Gould, M. N. Desvigne and A. E. Chaffin (2023). "Surgical Reconstruction of Stage 3 and 4 Pressure Injuries: A Literature Review and Proposed Algorithm from an Interprofessional Working Group." Advances in Skin & Wound Care 36(5): 249-258.

AROA BIOSURGERY LIMITED
Place, Airport Oaks, Auckland 2022, New Zealand
107111, Airport Oaks, Auckland 2150, New Zealand
AROABIO.COM

Cormican, M. T., N. J. Creel, B. A. Bosque, S. G. Dowling, P. P. Rideout and W. M. Vassy (2023). "Ovine Forestomach Matrix in the Surgical Management of Complex Volumetric Soft Tissue Defects: A Retrospective Pilot Case Series." ePlasty 23: e66

Bosque, B. A., S. G. Dowling, B. C. H. May, R. Kaufman, I. Zilberman, N. Zolfaghari, H. Que, J. Longobardi, J. Skurka, J. E. Geiger and M. M. Melin (2023). "Ovine Forestomach Matrix in the Surgical Management of Complex Lower-Extremity Soft-Tissue Defects: A Retrospective Multi-Center Case Series." J Am Podiatr Med Assoc 113(3): 22-081.

Duplechain, A. B., B. A. Bosque, C. W. Fligor and A. E. Chaffin (2023). "Soft Tissue Reconstruction With Ovine Forestomach Matrix After Wide Excision of Plantar Fibromatosis." ePlasty 2023(23): e20.

Taarea, R., A. Florence, B. Bendixen and C. A. Castater (2024). "Early Experience with Ovine Forestomach Matrix for the Reconstruction of Abdominal Defects following Emergency Open Abdomen Surgery at a Level 2 Trauma Center." Trauma Cases Rev 10(1): 102.

For conference proceedings and published review articles, visit: www.aroa.com

AROA BIOSURGERY LIMITED
Place, Airport Oaks, Auckland 2022, New Zealand
107111, Airport Oaks, Auckland 2150, New Zealand
AROABIO.COM

An Open Access Journal
...Committed to the free exchange of medical knowledge in a global community
www.eplasty.com

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

Jeremy Simcock, MBChB,[a] and Barnaby C. H. May, PhD[b]

[a]University of Otago Christchurch, Christchurch, New Zealand; and [b]Mesynthes Limited, Lower Hutt, New Zealand

Correspondence: barnaby.may@mesynthes.com

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

Published November 7, 2013

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,

An Open Access Journal
...Committed to the free exchange of medical knowledge in a global community
www.eplasty.com

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

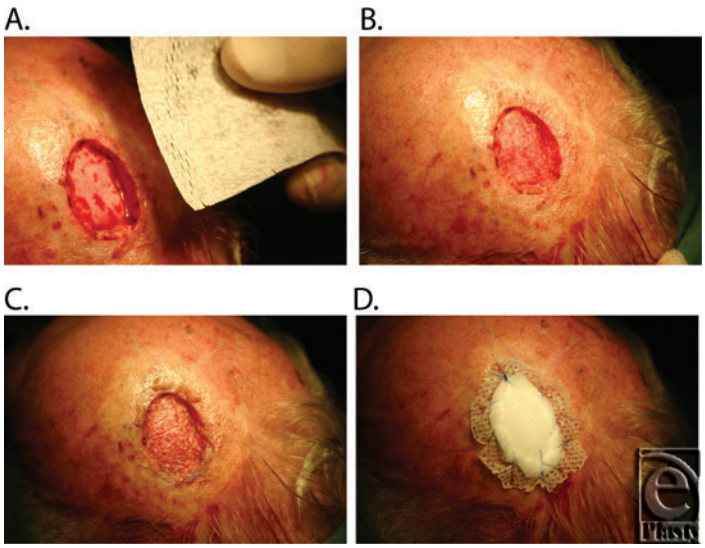


Figure 1. Representative images of the tumor resection and single-stage split-thickness grafting. (*a*) Excisional defect following tumor excision and meshed OFM prior to rehydration. (*b*) Rehydrated OFM cut to size and placed within the defect to conform to the underlying periosteum. (*c*) Meshed STSG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

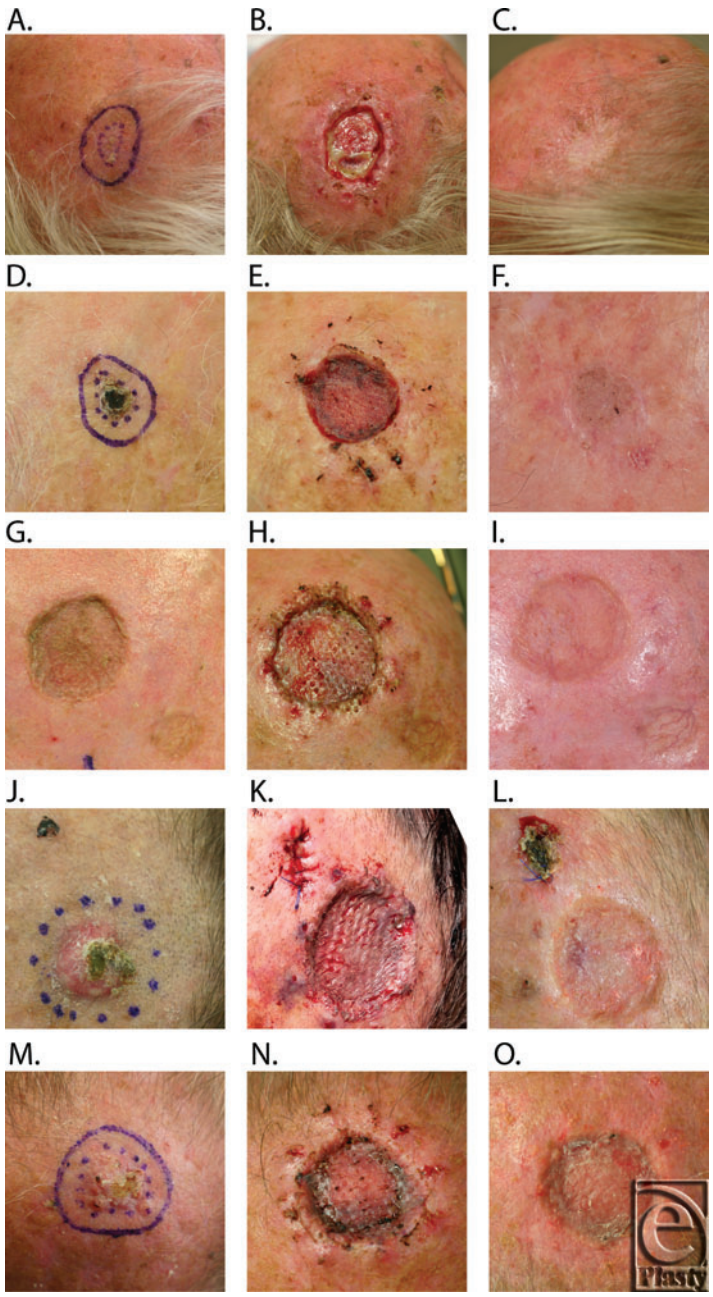


Figure 2. Representative images of the study participants B001 (2.A., 2.B., 2.C.), B002 (2.D., 2.E., 2.F.), B003 (2.G., 2.H., 2.I.), B004 (2.J., 2.K., 2.L.), and B005 (2.M., 2.N., 2.O.), prior to tumor excision (2.A., 2.D., 2.G., 2.J., 2.M.) and 1 week following surgery (2.B., 2.E., 2.H., 2.K., 2.N.).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

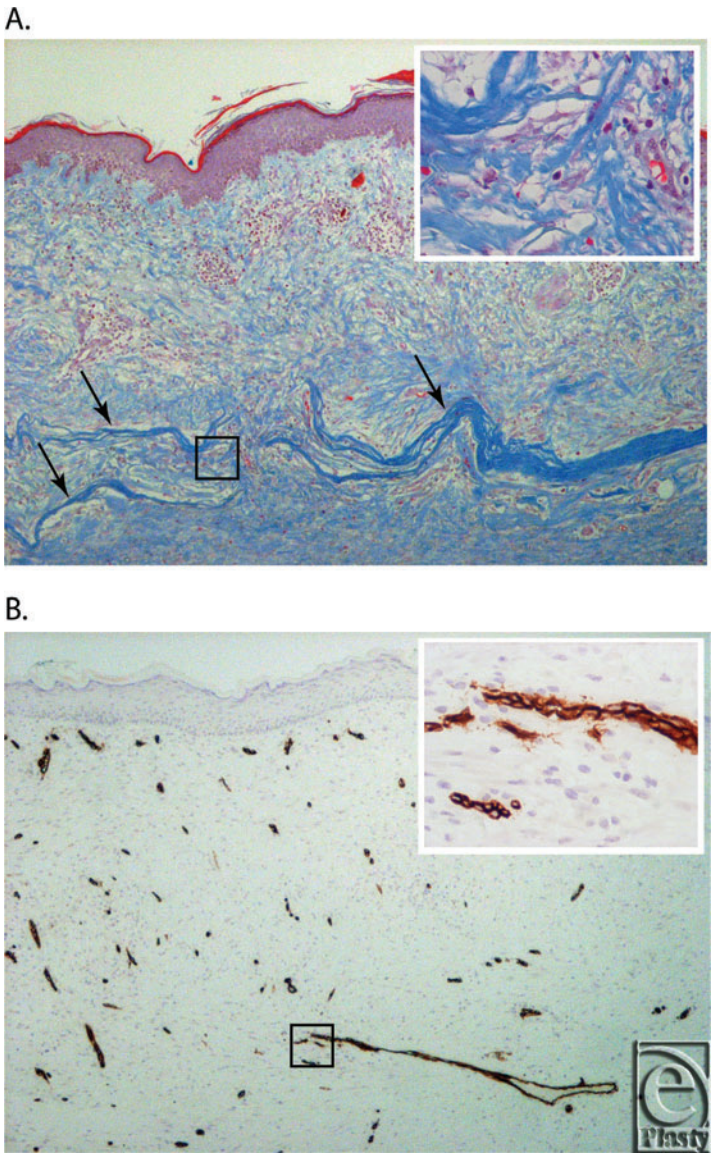


Figure 3. (*a*) Gomori's Trichome stain of the excised graft from B004, 4 weeks postgraft (4× magnification). Arrows indicate the intact fragments of OFM. Insert shows a 40× magnification of the area indicated by the black square. (*b*) CD34 immunohistochemistry of the excised graft from B004, 4 weeks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

Acknowledgements

The authors would like to acknowledge the clinical research assistance of Viki Robinson and the Pathology Department of Hutt Valley Hospital for histology and immunohistochemistry. B.C.H.M. is a shareholder in Mesynthes Limited.

REFERENCES

1. Wainwright DJ. Use of an acellular allograft dermal matrix (AlloDerm) in the management of full-thickness burns. *Burns.* 1995;21:243-48.
2. Callcut RA, Schurr MJ, Sloan M, Faucher LD. Clinical experience with Alloderm: a one-staged composite dermal/epidermal replacement utilizing processed cadaver dermis and thin autografts. *Burns.* 2006;32: 583-8.
3. Yim H, Cho YS, Seo CH, et al. The use of AlloDerm on major burn patients: AlloDerm prevents post-burn joint contracture. *Burns.* 2010;36:322-8.
4. Jung SN, Chung JW, Yim YM, Kwon H. One-stage skin grafting of the exposed skull with acellular human dermis (AlloDerm). *J Craniofac Surg.* 2008;19:1660-2.
5. Eo S, Cho S, Shin H, Kim JY. The utility of AlloDerm in hand resurfacing. *J Plast Reconstr Aesthet Surg.* 2009;63:e41-3.
6. Hayek B, Hatef E, Nguyen M, Ho V, Hsu A, Esmaeli B. Acellular dermal graft (AlloDerm) for upper eyelid reconstruction after cancer removal. *Ophthal Plast Reconstr Surg.* 2009;25:426-9.
7. Chun YS, Verma K. Single-stage full-thickness scalp reconstruction using acellular dermal matrix and skin graft. *Eplasty.* 2011;11:e4.
8. Kontos AP, Qian Z, Urato NS, Hassanein A, Proper SA. AlloDerm grafting for large wounds after Mohs micrographic surgery. *Dermatol Surg.* 2009;35:692-8.
9. Lun S, Irvine SM, Johnson KD, et al. A functional extracellular matrix biomaterial derived from ovine forestomach. *Biomaterials.* 2010;31:4517-29.
10. Irvine SM, Cayzer J, Todd EM, et al. Quantification of in vitro and in vivo angiogenesis stimulated by ovine forestomach matrix biomaterial. *Biomaterials.* 2011;32:6351-61.
11. Liden B, May BCH. Clinical outcomes following the use of ovine forestomach matrix (endoform dermal template) to treat chronic wounds: a case series. *Adv Skin Wound Care.* 2013;26:164-7.
12. Feierabend TC, Bindra RN. Injuries causing major loss of scalp. *Plast Reconstr Surg.* 1985;76:189-94.
13. Faulhaber J, Felcht M, Teerling G, et al. Long-term results after reconstruction of full thickness scalp defects with a dermal regeneration template. *J Eur Acad Dermatol Venereol.* 2010;24:572-7.
14. Badylak SF, Gilbert TW. Immune response to biologic scaffold materials. *Semin Immunol.* 2008;20:109-16.
15. Prevel CD, Eppley BL, Summerlin DJ, et al. Small intestinal submucosa: utilization as a wound dressing in full-thickness rodent wounds. *Ann Plast Surg.* 1995;35:381-8.

Extracellular matrix graft for the surgical management of Hurley stage III hidradenitis suppurativa: a pilot case series

Objective: Surgical management of Hurley stage III hidradenitis suppurativa (HS) typically involves the excision of diseased tissue and subsequent reconstruction, potentially leading to complications or recurrence of the disease. This pilot case series sought to evaluate a decellularised ovine forestomach matrix (OFM) extracellular matrix (ECM) graft for soft tissue regeneration as part of surgical reconstruction of stage III HS of the axilla.
Method: The prospective pilot case series involved six participants and a total of eight defects. The ECM graft was used either as a dermal substitute for a staged reconstruction (n=3 defects) or as an implant under a fasciocutaneous flap (n=5 defects) following wide excision of the diseased tissue.
Results: In all cases complete healing was achieved, with no major surgical complications. When used as a dermal substitute the OFM graft was completely granulated within 2–4 weeks, with defects closing by secondary intention or following placement of a split-thickness skin graft. When used as an implant beneath a fasciocutaneous flap, healing of the surgical sites was observed after 1–3 months. At the long-term follow-up (3–12 months), all participants had excellent range of motion and none had reported disease recurrences.
Conclusion: This pilot case series explored the implementation of an ECM graft as part of the surgical management of axilla Hurley stage III HS. Although the study had a limited number of participants, long-term outcomes were promising and suggest further studies are warranted.
Declaration of interest: The graft (Myriad Soft Tissue Matrix) was provided by Aroa Biosurgery Limited (Auckland, New Zealand). AEC has received educational travel grants from Aroa Biosurgery Limited. The authors have no conflicts of interest to declare.

dermal substitute • flap reconstruction • hidradenitis suppurativa • ovine forestomach matrix

Hidradenitis suppurativa (HS) is a debilitating, chronic inflammatory disease of the dermis.[1] The causes of HS may be a combination of genetic, endocrine, environmental and microbial factors.[2] Disease progression involves follicular occlusion caused by inflammation, hyperkeratosis and hyperplasia of sweat glands, and can lead to multiple abscesses and cysts in the affected area.[2] Histological changes in HS versus normal tissue include a thickening of the epidermis, high cellular infiltration around hair follicles and disorganised collagen fibres with a decrease in collagen III.[3] Overall, systemic inflammatory markers are higher in HS than non-HS dermal diseases, such as psoriasis.[4]

Treatment of HS depends on disease severity (i.e., Hurley stage I, II and III) and includes medical treatments (for example, antibiotics, steroids and anti-inflammatories), as well as surgical interventions to remove the diseased tissue.[2] Recurrence is lower when therapeutic and surgical approaches are combined, compared with surgery alone.[5] Surgical intervention for HS depends on the severity of the disease. In mild cases, local excision or deroofing of abscesses and sinuses may be sufficient.[6] In severe cases of HS (for example, Hurley stage III) that include diffuse interconnecting tracts and abscesses across a large area, a significant surgical intervention is required, such as wide excision of the diseased tissue.[6] Following wide excision, several reconstructive approaches are possible, including primary closure, healing via secondary intention, split-thickness skin grafting, local and free flaps.[7] Recurrence rates after a wide excision appear lower than after local excision;[5] however, the extent of tissue removal means that healing time is longer and complications more likely. Bouazzi et al.[8] found that complication rates and recurrence rates remain relatively high at 25.1% and 14.0%, respectively. Ovadja et al.[9] estimated recurrence rates for wide and partial excisions at 5% and 26%, respectively, from a meta-analysis of 125 articles. Complications associated with reconstruction after wide excision may be attributed to the poor quality of the underlying tissues (for example, fibrotic or inflamed tissue), potential for dead space between the advancing flap and underlying tissues, poor vascularity of the tissues, and associated patient comorbidities.

Ovine forestomach matrix (OFM) is an extracellular matrix (ECM) bioscaffold widely used in wound management and implant procedures.[10–13] OFM has excellent biophysical performance,[14] is anti-inflammatory,[15,16] recruits mesenchymal stem cells,[17] stimulates angiogenesis,[18] aids tissue infill and undergoes complete remodelling.[18] OFM is available as a graft (Myriad Soft Tissue Matrix, Aroa Biosurgery Limited, New Zealand) designed as a dermal substitute

Abigail E Chaffin,[1] MD, FACS, CWSP, FAPWCA, Associate Professor of Surgery and Program Director*; **Marie-Claire Buckley**,[2] MD, Assistant Professor*
***Corresponding author email:** achaffin@tulane.edu
1 Department of Surgery, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, Louisiana 70112, US. **2** Department of Surgery, University of Minnesota, School of Medicine, Minneapolis, 55455, US.

for the surgical management of deep partial or full-thickness defects in plastic and reconstructive surgery and for implant procedures to reinforce soft tissues. Given OFM's anti-inflammatory properties and ability to quickly build new tissue, we hypothesised that the OFM graft may have utility as part of surgical reconstruction of HS. In this pilot case series, patients with Hurley stage III HS of the axilla were surgically reconstructed using the OFM graft, either as a dermal substitute or as an implant as part of a flap reconstruction of the affected areas.

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. Participants who were unwilling to follow the study protocol or unable to provide informed consent were excluded from it.

A total of six patients consented to participate in this case series (Table 1). All patients had a history of axillary HS and had previously been managed with various interventions, including standard wound care, topical antibacterials, minor surgical deroofings, laser treatments, antibiotics and anti-inflammatory therapies. Of the patients, two (Participants 2 and 6) presented with bilateral lesions that were simultaneously managed as part of the case series. None of the patients were receiving pharmacotherapies for their HS management at the time of the surgery or during the follow-up period. Reconstruction proceeded either using the OFM graft (Myriad Soft Tissue Matrix) as a dermal substitute or as part of a flap reconstruction (Table 1). When used as a dermal substitute (Participants 1 and 2), lesions were resected including the deep subcutaneous fat layer down to the fascia. OFM graft was cut to size and rehydrated, then sutured to the perimeter of the defect. Either the three-layer ('Thin') or five-layer ('Thick') OFM graft was used (Table 1). A non-adherent dressing (Adaptic, KCI Corporation, US) was placed, then negative-pressure wound therapy (NPWT) was maintained for 1–2 weeks (continuous 125mmHg). Once the OFM graft had fully granulated, the defects were managed with either a combination of ECM (Endoform Natural Dermal Template, Aroa Biosurgery Limited, New Zealand) and gentian violet/methylene blue (GV/MB) foam dressing (Hydrofera Blue, Hydrofera

Table 1. Participant summary including demographic, surgical management and outcomes

Participant, gender, age, comorbidities	HS stage III duration	Location	Surgical management	Time of last follow-up
Participant 1 Male, 29 Deep vein thrombosis (DVT)	2 years	Right axilla	• Resected down to fascia, ~12×7cm defect • ECM graft applied as a dermal substitute • Fully granulated at 4 weeks • ~80% epithelialised at 6 weeks	Minor complication at 1 week – resolved week 2 11+ months No further complications No recurrence
Participant 2 Male, 39 Uncontrolled diabetes Smoker HbA1c=12.6%	15 years	Right and left axilla	• Wide resection down to fascia, ~12×17cm (right) and ~12×20cm (left) defects • ECM graft applied as a dermal substitute • Fully granulated at 3 weeks • STSG at 22 weeks, 100% graft take at 23 weeks	7+ months No complications No recurrence
Participant 3 Female, 31	5 years	Right axilla	• Partial axillary resection, ~15x15cm defect • ECM graft placement, then fasciocutaneous flap reconstruction • Fully healed at 1 month	12+ months No complications No recurrence
Participant 4 Female, 26 HIV	5 years	Right axilla	• Entire hair-bearing axillary resection, ~10x20cm defect • ECM graft placement, then fasciocutaneous flap reconstruction • Fully healed at 3 months	Minor complication at week 3 – resolved week 6 10+ months No further complications No recurrence
Participant 5 Female, 37 Gout	10 years	Right axilla	• Entire hair-bearing axillary resection, ~15×20cm defect • ECM graft placement, then fasciocutaneous flap reconstruction • Fully healed at 3 months	7+ months No complications No recurrence
Participant 6 Female, 30 Lupus, rheumatoid arthritis	10 years	Right and left axilla	• Entire hair-bearing axillary resection, ~8×12cm defects • ECM graft placement, then fasciocutaneous flap reconstruction • Fully healed at 1 month	3+ month No complications No recurrence

ECM—extracellular matrix; HS—hidradenitis suppurativa; STSG—split-thickness skin graft

Corporation, US), or polyhexamethylene biguanide (PHMB) dressing (Bioguard, Integra Life Sciences Corporation, US). Of the patients, one (Participant 1) closed via secondary intention, while another received a split-thickness skin graft (STSG) (Participant 2). Flap reconstruction (Participants 3–6) used a wide excision of the affected tissue as well as lateral margins down to the fascia. OFM graft was cut to size, rehydrated and placed into the defect, before a fasciocutaneous flap advancement and closure. Iodoform gauze was packed between sutures, and a non-adherent dressing placed, followed by GV/MB foam and silver alginate dressings. Sutures were removed at week five. All surgical sites were monitored weekly by the investigators.

Results

Patients with Hurley stage III HS of the axilla underwent wide excision of the hair-bearing area of the axilla down to the fascia, leaving defects with sizes ranging from ~100–300cm^2 (Table 1). Where the OFM graft was used as a dermal substitute (Participants 1 and 2; n=3 sites), the OFM grafts became infiltrated and vascularised after ~1 week, and completely granulated at 2–4 weeks. Where the OFM graft was implanted under a fasciocutaneous flap (Participants 3–5), the surgical sites were healed after 1–3 months. Of the patients, one (Participant 4) experienced mild wound dehiscence at three weeks that closed with standard management. Of the six patients reported in the case series, none experienced a recurrence at the last postoperative visit at 3–12 months.

Patient 1

A 29-year-old male patient presented with two years of Hurley stage III HS of the right axilla. Full-thickness wide excision down to the fascia was performed, leaving a defect of ~12×7cm (Fig 1). The defect was reconstructed using OFM graft ('Thick', 10×20cm) as a dermal substitute to build granulation tissue in the defect and enable closure via secondary intention. The OFM graft was dressed with a non-adherent dressing and NPWT (125mmHg, continuous) used for the first 1.5 weeks, then a PHMB dressing used until closure. At day four, the OFM graft was visibly integrating as granulation tissue formed, with only the distal portion that was not contacting the underlying tissue not showing vascularity. At one week the outer layers of the graft had become contaminated and had sloughed from the remainder of the defect. These were removed via gentle debridement. The surface of the graft was lightly debrided at 1.5 weeks to reveal a well vascularised granulation bed and NPWT was discontinued. At week four the granulated defect had started to epithelialise and by week eight the defect was 80% epithelialised and the patient returned to work. There was no recurrence at the last follow-up, at 7.5 months, and the patient had good range of motion and acceptable cosmesis.

Fig 1. Reconstruction of axilla hidradenitis suppurativa using ovine forestomach matrix (OFM) graft as a dermal substitute following wide excision of the axilla (Participant 1). Initial defect site (**a**). Surgical excision of damaged tissue (~12×7cm) (**b**). OFM graft placement and fixation with staples (**c**). Day 4 post-operation, small areas of granulation tissue present (**d**). Day 10, granulation tissue apparent (**e**). Week 4 post-operation (**f**). Week 8 post-operation (**g**)

Patient 2

A 39-year-old male patient, with uncontrolled diabetes and a heavy smoker presented with bilateral HS lesions to the axilla (Fig 2). The patient underwent a wide excision down to the fascia, leaving excision sites of 17×12cm (right) and 20×12cm (left). OFM graft ('Thin') was trimmed to size, rehydrated and placed into the defect. The grafts were sutured to the perimeter of the defect and additional mattress sutures placed in the centre of the graft to tightly approximate this to the underlying tissue. The grafts were dressed with a non-adherent contact layer, then NPWT (125mmHg, continuous) used for 1.5 weeks. The grafts were 100% granulated at three weeks, but an STSG was deferred until the patient's diabetes and nicotine use were controlled. Instead, ECM wound dressing (Endoform Natural, Aroa Biosurgery Limited) was applied weekly to aid epithelialisation of the granulation tissue, covered with a GV/MB foam. At 15 weeks the right and left defects had reduced to 5.6×11cm and 3.5×11cm, respectively, and at 22 weeks STSGs were placed on the bilateral axillae, with 100% graft take at 23 weeks. Both defects were healed by week 26.

Patient 3

A 31-year-old female patient presented with five years of Hurley stage III HS of the axilla. Full-thickness excision down to the fascia was performed under general anaesthetic leaving a defect of ~15×15cm (Fig 3). OFM graft was trimmed to size, rehydrated in saline then applied to the excision site and sutured in place with absorbable sutures before fasciocutaneous

Fig 2. Bilateral reconstruction of axilla hidradenitis suppurativa using ovine forestomach matrix (OFM) graft as a dermal substitute (Participant 2). Surgical sites on the right (R) and left (L) axilla. Defect sizes were 17×12cm and 20×12cm, respectively (**a**). Surgical excision (**b**). OFM graft placement and fixation with sutures at the periphery and mattress sutures at the centre (**c**). At three weeks post-operation, 100% granulation tissue (**d**). At 15 weeks post-operation and weekly extracellular matrix (ECM) treatment, defects reduced in size to 5.6×11cm (R) and 3.5×11cm (L) (**e**). At 22 weeks post-operation, before placement of split-thickness skin graft (not shown) (**f**)

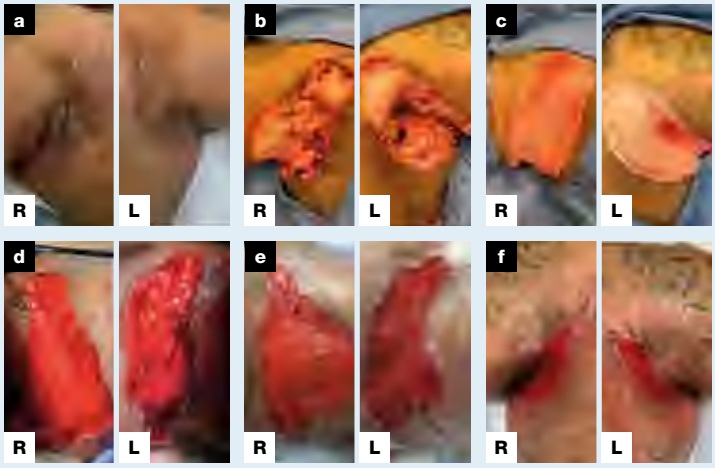
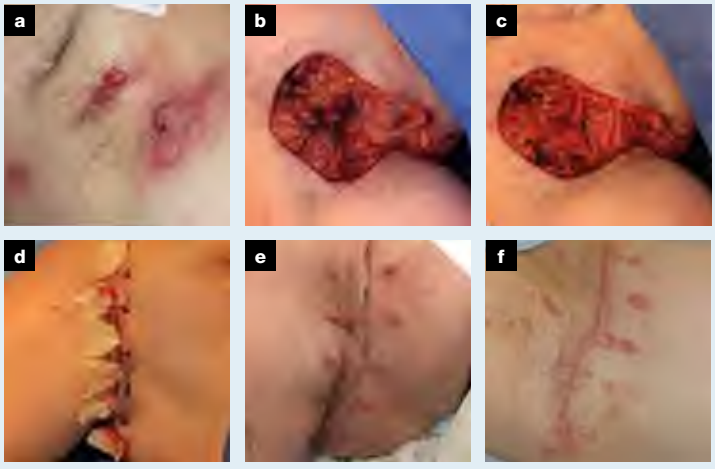


Fig 3. Fasciocutaneous flap reconstruction of axilla hidradenitis suppurativa using ovine forestomach matrix (OFM) graft as an implant device (Participant 3). HS of axilla tissue pre-operation (**a**). Partial excision of axilla tissue (~15×15cm) (**b**). OFM graft sutured to fascia underneath flap advancement (**c**). Flap advancement and closure with Iodoform packing between adjacent sutures (**d**). Week 3 post-operation, sutures removed (**e**). Week 11, wound healed (**f**)



flap advancement and closure. Iodoform was packed between adjacent sutures to enable any fluid to wick from the defect. The site was dressed with a non-adherent and GV/MB antibacterial foam dressing. Sutures were removed at week three and by week 11 the surgical site was completely healed. No complications or recurrences were noted, and the surgical site was covered with a secondary dressing. Healing of the surgical site was observed at three weeks and no complications or recurrence was noted at seven months.

Patient 4

A 26-year-old female presented with five years of Hurley stage III HS of the axilla with multiple draining and interconnected sinuses. The patient had well-controlled HIV, and had previously managed HS with topical antibiotics and laser treatments. Full-thickness excision of the affected area was performed leaving a defect of ~20×10cm (Fig 4). OFM graft ('Thick', 10×20cm) was placed in the defect and fixed in place with absorbable sutures before a fasciocutaneous flap advancement and closure. Iodoform was packed between pledgeted retention sutures and the defect covered with a non-adherent GV/MB dressing. The patient presented at week three with a wet cover dressing after trying to self-manage dressing changes, resulting in minor dehiscence of the closure and maceration. The area of dehiscence was gently debrided and granulation tissue was noted in the base of the defect. The area of dehiscence was managed with ECM and GV/MB. By week six, only a small (~2×2cm) area of dehiscence remained open and by week 12 the entire area was fully healed. The patient's axilla remains lesion free at seven months.

Discussion

This case series gave preliminary insights into the successful surgical management of Hurley stage III HS using OFM graft either as a dermal substitute or as part of a flap reconstruction. Surgical removal of diseased tissue in a Hurley stage III HS patient results in a large tissue deficit at the surgical site, leaving patients at risk of postoperative complications. Additionally, many patients with HS display comorbidities, such as obesity, metabolic syndrome and insulin resistance, which can reduce normal healing rates post-surgery.[19] Tissue within HS lesions presents many histological findings that are associated with uncontrolled inflammation, such as lymphocyte infiltration and scar tissue, including a decrease in collagen III.[3] Interestingly, circulating matrix metalloproteinases (MMPs) are increased in the blood of an HS patient and it is thought that MMPs facilitate the rupture of neighbouring follicles within lesions, leading to tunnelling and abscess formation.[20] As such, HS-affected tissues may be predisposed to poor healing and present a real challenge in surgical reconstruction.

Decellularised ECM bioscaffolds, such as OFM, that are typically produced from human or animal tissues, have been shown to increase the rate of healing in hard-to-heal wounds, and it is thought that this is due to the material's ability to promote angiogenesis, control inflammation and provide a structural scaffold for remodelling.[15,16,18,21] As it relates to the pathology seen in HS, studies have shown that an important factor in ECM bioscaffold-mediated healing is the impact on chronic inflammation.[22] ECM bioscaffolds can promote constructive remodelling by changing the

phenotype of inflammatory cells, leading to an increase in the population of macrophages that display a remodelling anti-inflammatory phenotype (M2) versus a pro-inflammatory phenotype (M1).[15,23] The OFM bioscaffold has been shown to inhibit MMPs and neutrophil elastase,[16] and undergoes constructive remodelling *in vivo*, consistent with an anti-inflammatory response.[15,18,24]

Wide excision of HS-affected tissue leaves a significant full-thickness defect which, left to heal via secondary intention, may result in significant scar contracture and loss of functional status of the affected area. Dermal substitutes have been part of the reconstructive ladder for many years, although their use in HS reconstruction is limited relative to their widespread use in applications such as burns, necrotising fasciitis, trauma and wounds. Iida et al. reported a two-stage procedure using a bovine dermal substitute (Terudermis, Terumo Corporation, Japan) following wide excision of axillary HS in three patients.[25] Gonzaga et al. took a similar two-stage approach in four patients using a bi-layer dermal matrix (Integra, Integra Life Sciences Corporation, US), but included NPWT to aid regeneration of the neodermis, prior to STSG.[26] The largest case report included 18 patients (33 lesions) using a bi-layer dermal matrix (Integra) followed by STSG, though local infection was observed in 45% of patients following use of the bi-layer dermal matrix.[27] Nicoli et al. combined the use of platelet rich plasma and a hyaluronic acid dermal substitute (Hyalomatrix Fidia Advanced Biopolymers, Italy) following wide excision, leaving the defect to close via secondary intention.[28] When used as a dermal substitute, the OFM graft showed rapid granulation tissue formation (~1 week), and defects went on to close either via secondary intention (Participant 1) or received an STSG (Participant 2).

The OFM graft was alternatively used as an implant as part of a fasciocutaneous flap reconstruction (Participants 3–5). The option for a flap reconstruction was dependent on the availability of proximal tissues. Flap reconstructions of HS have been widely reported, but often suffer complications.[5,8,9] Flap dehiscence and associated complications may be explained by the chronicity of the underlying tissues, poor vascularity, and potential for dead space between the flap and the underlying fascial layer. It was hypothesised that placement of an ECM bioscaffold as an implant under the fasciocutaneous flap may reduce these complications as the graft would be infiltrated and remodelled to provide a deeper layer of well-vascularised new tissue. All patients managed using this approach healed well.

Fig 4. Flap reconstruction of axilla hidradenitis suppurativa (HS) using ovine forestomach matrix (OFM) graft as an implant under the fasciocutaneous flap (Participant 4). HS tissue of the axilla (**a**). Full-thickness excision of damaged tissue (~20×10cm) (**b**). OFM graft placement and fixation before flap advancement (**c**). Flap advancement and primary closure with Iodoform packed between pledgeted retention sutures (**d**). Week 1, post-operation (**e**). Week 3, minor post-operation dehiscence treated with ECM (**f**). Week 5 post-operation (**g**). Week 6, small area of dehiscence open (~2×2cm) (**h**). Week 12, entire area fully healed (**i**)

A patient (Participant 4) had dehiscence of the closure at week three, due to poor dressing management.

Conclusion

Patients with HS experience significant challenges with regard to their quality of life, such as an increased risk of cardiovascular disease and suicide, sexual dysfunction, irritable bowel syndrome, depression and anxiety.[29] Surgical intervention can risk further challenges without appropriate tools to reduce the number of complications and recurrence of lesions. Our initial findings, using the OFM graft as part of our surgical reconstruction of these affected patients, is very encouraging. A larger case study with long-term follow-up of patients treated with OFM graft would be a valuable tool to access improvements in the rate of recurrence of the disease and complications after surgical intervention with OFM. JWC

Acknowledgements: The authors would like to acknowledge Aroa Biosurgery Limited (New Zealand) for assistance in the preparation of this manuscript.

References

1 Duran C, Baumeister A. Recognition, diagnosis, and treatment of hidradenitis suppurativa. JAAPA 2019; 32(10):36–42. https://doi.org/10.1097/01.JAA.0000578768.62051.13
2 Seyed Jafari SM, Hunger RE, Schlapbach C. Hidradenitis suppurativa: current understanding of pathogenic mechanisms and suggestion for treatment algorithm. Front Med (Lausanne) 2020; 7:68. https://doi.org/10.3389/fmed.2020.00068
3 Nisar S, Roberson JL, Carney BC et al. Further histological and cellular characterization of hidradenitis suppurativa in 11 patients. Eplasty 2019; 19:e21
4 Riis PT, Soeby K, Saunte DM, Jemec GB. Patients with hidradenitis suppurativa carry a higher systemic inflammatory load than other dermatological patients. Arch Dermatol Res 2015; 307(10):885–889.

Reflective questions

- Hidradenitis suppurativa (HS) has a significant impact on patients' quality of life and often patients with HS simply manage the symptoms associated with HS lesions. Should surgical intervention be considered more often for these patients, especially in instances of stage III HS?
- Surgical reconstruction involving inflamed tissue like that seen in HS often suffers from increased complication rates (eg infection, dehiscence or seroma). Should the inclusion of advanced ECM technology to counteract tissue inflammation be considered more often for these types of surgeries?

https://doi.org/10.1007/s00403-015-1596-5
5 Mehdizadeh A, Hazen PG, Bechara FG et al. Recurrence of hidradenitis suppurativa after surgical management: a systematic review and meta-analysis. J Am Acad Dermatol 2015; 73(5 Suppl 1):S70–S77. https://doi.org/10.1016/j.jaad.2015.07.044
6 Saunte DML, Jemec GBE. Hidradenitis suppurativa: advances in diagnosis and treatment. JAMA 2017; 318(20):2019–2032. https://doi.org/10.1001/jama.2017.16691
7 Scuderi N, Monfrecola A, Dessy LA et al. Medical and surgical treatment of hidradenitis suppurativa: a review. Skin Appendage Disord 2017; 3(2):95–110. https://doi.org/10.1159/000462979
8 Bouazzi D, Chafranska L, Saunte DML, Jemec GBE. Systematic review of complications and recurrences after surgical interventions in hidradenitis suppurativa. Dermatol Surg 2020; 46(7):914–921. https://doi.org/10.1097/DSS.0000000000002323
9 Ovadja ZN, Jacobs W, Zugaj M, van der Horst C, Lapid O. Recurrence rates following excision of hidradenitis suppurativa: a systematic review and meta-analysis. Dermatol Surg 2020; 46(8):e1–e7. https://doi.org/10.1097/DSS.0000000000002403
10 Bohn GA, Gass K. Leg ulcer treatment outcomes with new ovine collagen extracellular matrix dressing: a retrospective case series. Adv Skin Wound Care 2014; 27(10):448–454. https://doi.org/10.1097/01.ASW.0000453728.12032.6f
11 Lullove EJ. 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. Wounds 2017; 29(4):107–114
12 Simcock JW, Than M, Ward BR, May BC. Treatment of ulcerated necrobiosis lipoidica with ovine forestomach matrix. J Wound Care 2013; 22(7):383–384. https://doi.org/10.12968/jowc.2013.22.7.383
13 Ferzoco SJ. Early experience outcome of a reinforced bioscaffold in inguinal hernia repair: a case series. Int J Surg Open 2018; 12:9–11. https://doi.org/10.1016/j.ijso.2018.06.001
14 Floden EW, Malak SF, Basil-Jones MM et al. Biophysical characterization of ovine forestomach extracellular matrix biomaterials. J Biomed Mater Res B Appl Biomater 2011; 96(1):67–75. https://doi.org/10.1002/jbm.b.31740
15 Street M, Thambyah A, Dray M et al. Augmentation with an ovine forestomach matrix scaffold improves histological outcomes of rotator cuff repair in a rat model. J Orthop Surg Res 2015; 10:165. https://doi.org/10.1186/s13018-015-0303-8
16 Negron L, Lun S, May BCH. Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. Int Wound J 2014; 11(4):392–397. https://doi.org/10.1111/j.1742-481X.2012.01106.x
17 Dempsey SG, Miller CH, Schueler J et al. A novel chemotactic factor derived from the extracellular matrix protein decorin recruits mesenchymal stromal cells in vitro and in vivo. PLoS One 2020; 15(7):e0235784. https://doi.org/10.1371/journal.pone.0235784
18 Irvine SM, Cayzer J, Todd EM et al. Quantification of in vitro and in vivo angiogenesis stimulated by ovine forestomach matrix biomaterial. Biomaterials 2011; 32(27):6351–6361. https://doi.org/10.1016/j.biomaterials.2011.05.040
19 Vilanova I, Hernandez JL, Mata C et al. Insulin resistance in hidradenitis suppurativa: a case–control study. J Eur Acad Dermatol Venereol 2018; 32(5):820–824. https://doi.org/10.1111/jdv.14894
20 Sabat R, Jemec GBE, Matusiak L, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. Nat Rev Dis Primers 2020; 6(1):18. https://doi.org/10.1038/s41572-020-0149-1
21 Lun S, Irvine SM, Johnson KD et al. A functional extracellular matrix biomaterial derived from ovine forestomach. Biomaterials 2010; 31(16):4517–4529. https://doi.org/10.1016/j.biomaterials.2010.02.025
22 Bohn GA, Schultz GS, Liden BA et al. Proactive and early aggressive wound management: a shift in strategy developed by a consensus panel examining the current science, prevention, and management of acute and chronic wounds. Wounds 2017; 29(11):S37–S42
23 Badylak SF, Valentin JE, Ravindra AK et al. Macrophage phenotype as a determinant of biologic scaffold remodeling. Tissue Eng Part A 2008; 14(11):1835–1842. https://doi.org/10.1089/ten.tea.2007.0264
24 Overbeck N, Nagvajara GM, Ferzoco S et al. In-vivo evaluation of a reinforced ovine biologic: a comparative study to available hernia mesh repair materials. Hernia 2020. https://doi.org/10.1007/s10029-019-02119-z
25 Iida N, Fukushima K, Kanzaki A. A two-stage technique using a bovine dermal substitute to treat axillary hidradenitis. Eur J Plast Surg 2005; 28:359–363. https://doi.org/10.1007/s00238-005-0784-5
26 Gonzaga TA, Endorf FW, Mohr WJ, Ahrenholz DH. Novel surgical approach for axillary hidradenitis suppurativa using a bilayer dermal regeneration template: a retrospective case study. J Burn Care Res 2013; 34(1):51–57. https://doi.org/10.1097/BCR.0b013e31826a7be7
27 Yamashita Y, Hashimoto I, Matsuo S et al. Two-stage surgery for hidradenitis suppurativa: staged artificial dermis and skin grafting. Dermatol Surg 2014; 40(2):110–115. https://doi.org/10.1111/dsu.12400
28 Nicoli F, Balzani A, Lazzeri D et al. Severe hidradenitis suppurativa treatment using platelet-rich plasma gel and Hyalomatrix. Int Wound J 2015; 12(3):338–343. https://doi.org/10.1111/iwj.12117
29 Tzellos T, Zouboulis CC. Review of comorbidities of hidradenitis suppurativa: implications for daily clinical practice. Dermatol Ther (Heidelb) 2020; 10(1):63–71. https://doi.org/10.1007/s13555-020-00354-2

Using Ovine Extracellular Matrix in Difficult to Close Excisions of Common Skin Cancer: an Evolving New Technique

Gregory A Bohn, MD, FACS, ABPM/UHM
Medical Doctor
Board Certified by American Board of Surgery
Associate Professor of Surgery
Central Michigan University
Tawas City, MI, USA

ABSTRACT

Squamous cell (SCC) and basal cell (BCC) skin cancer are common presentations in elderly patients. Skin cancer are often located in sun exposed areas where damage from exposure has occurred. The sun exposed areas are often difficult to close or would require more complex measures to cover. Skin grafts or rotation flaps are commonly employed for coverage. Having tumor free margins is required to anticipate avoiding local recurrence. Mohs techniques examine the surgical margin to ensure that lesions are completely excised. When reliable frozen section is not available for immediate confirmation, permanent section may be used. Excising lesions and implementing radial identification allows margin localization of involved margins for re-excision. Divided into quartets, directed re-excision can be undertaken with minimal disturbance to the healing wound bed. Use of an ECM device (Myriad™, Aroa Biosurgery, Auckland, New Zealand) accelerates healing and leaves a cosmetically acceptable result that affords margin examination and re-excision with minimal disturbance to healing wound. Here we present an evolving technique of excision of common skin cancers utilizing ECM Matrix Graft technology and healing. This technique affords margin identification utilizing permanent section examination. Subsequent margin identification and re-excision if necessary is localized to individual quadrants of the excision site allowing more precise re-excision and not disturbing the grafted wound site. Healing seems accelerated and cosmetic appearance is acceptable to patients.

INTRODUCTION

Surgical excision of common skin cancers continues to evolve in technique. The introduction of readily available and cost effective Extracellular Matrix Grafts (Myriad™, Aroa Biosurgery, Auckland, New Zealand) that orchestrate healing can be integrated into a treatment plan in difficult to close skin cancer excisions. Certain areas of the body do not lend themselves to simple closure without tension and a high risk of dehiscence leaving an open wound. Immediate grafting or flap closure carries with it the chance that permanent sections of the margins could be found involved with micro extensions of tumor.[1-3] These micro extensions then raise the risk of local recurrence. Re-excision of a positive margin at an excision site where a skin graft was applied risks the skin graft to disruption and failure. It is likely that the graft will not be mobile enough to cover the excised area without undermining the graft from its new attachments. The graft of a re-excision is more

likely to heal with a tissue deformity at the operative site. Additionally, finding a positive margin in the pathology after flap closure is further complicated by locating with certainty the exact point of the involvement given the re-arrangement of tissue.[3] By incorporating an of the shelf ECM graft device, surgical excision can be completed and the excised area can be grafted with an Extracellular Matrix Graft Device immediately.[4] Permanent section evaluation and review can then be completed. If margins are incompletely excised, i.e., positive, directed and limited re-excision can be performed. Re-excision has not lead to a delay in healing. Once removed, the newly created defect can then be grafted by adding ECM graft material to the defect, filling the void and complement healing. In this way, surgically applied skin and rotated skin flaps are not disturbed or compromised as would be the case when re-excision after those more involved procedures are performed. In the event that grafting or flap closure is warranted, the use of an Extracellular Matrix Device does not preclude subsequent procedures from being utilized.[4] In the event of simple skin grafting, a granulated bed can be achieved with the use of an ECM graft device which would more readily accept a skin graft.

MATERIALS AND METHODS

The area about the skin cancer can be mapped out for resection. Using a 4 mm margin, the skin lesions can be excised full thickness to include epidermis, dermis and subcutaneous tissue.[1,5,6] Where appropriate, underlying fascia or other connective tissue can be removed en bloc.[1,5-10] The tissue specimen would then be prepared for quadrant margin examination.[2] The specimen can be oriented to identify each quadrant margin in a clockwise fashion. The specimen is oriented identifying the 12 to 3 quadrant, the 3 to 6 quadrant, the 6 to 9 quadrant, and the 9 to 12 quadrant margins for examination.[11-13] The quadrants are separated by notching with the scalpel to further separate the individual quadrants during examination. Sutures are used to identify each individual quadrant so that each unique margin can be identified by the pathologist and separated from each of the other quadrant margins. Each quadrant margin is uniquely identified, as demonstrated in Fig. 1. The specimen is then examined microscopically by means of permanent section. Each distinct margin edge can then be identified as part of the specimen evaluation and noted by specific quadrant. Paraffin block permanent section examination was utilized with anticipation that in the event of a positive quadrant margin, repeat resection could be more specifically identified and directed to remove margin edge in that quadrant with minimal disturbance to the ECM tissue device graft. This method avoids incongruity between frozen section evaluation and subsequent permanent sections.

At the time of excision, the tumor and resection margins are mapped out to allow for an adequate margin (Fig. 2a). Wide excision of the lesion is performed taking full-thickness tissue to obtain a deep margin as well as skin margin (Fig. 2c).

After skin tumor removal, the full thickness defect is then filled with a layered ECM-device tissue graft (Myriad™, Aroa Biosurgery) tailored such that it fits and fills the tissue defect (Fig. 2c,d). The ECM tissue device graft is then secured about its perimeter with an absorbable 4-0 monofilament suture. The ECM tissue device graft would be hydrated with saline solution. With placement and hydration, the ECM device absorbs blood elements into the graft from the surrounding tissues as visually noted by its red color (Fig. 3A-C). A bolster tie over dressing constructed of antibiotic impregnated petrolatum gauze and cotton

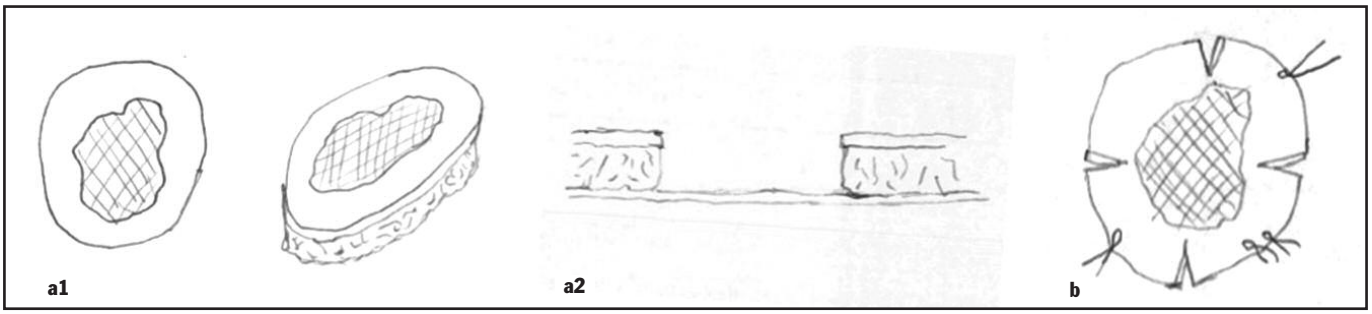


Figure 1. (a1, a2) Complete full-thickness excision planned with appropriate margins. (b) Specimen oriented and knotched to identify margins.

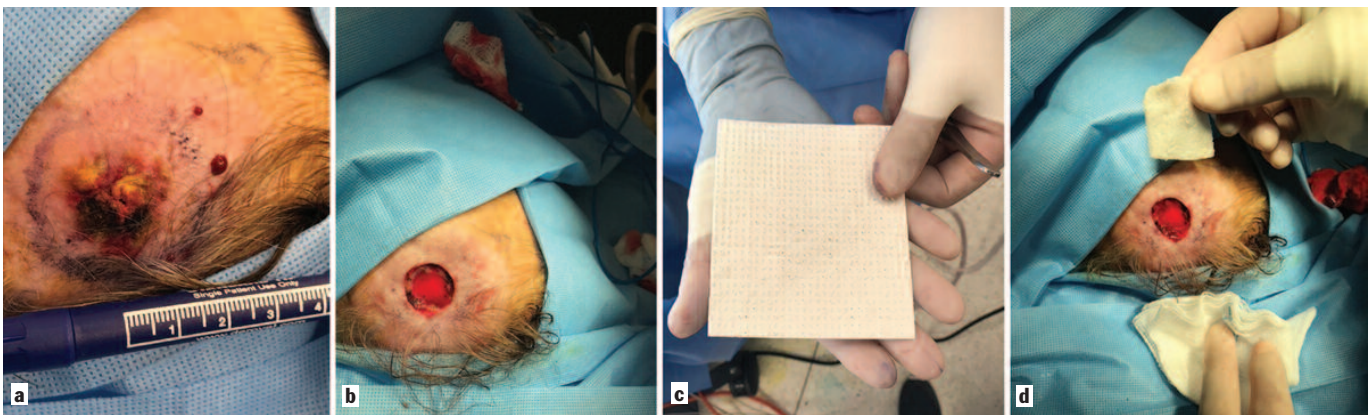


Figure 2. (a) Mapping and measuring resection margin. (b) Excision. (c,d) Layering of ECM tissue device graft.

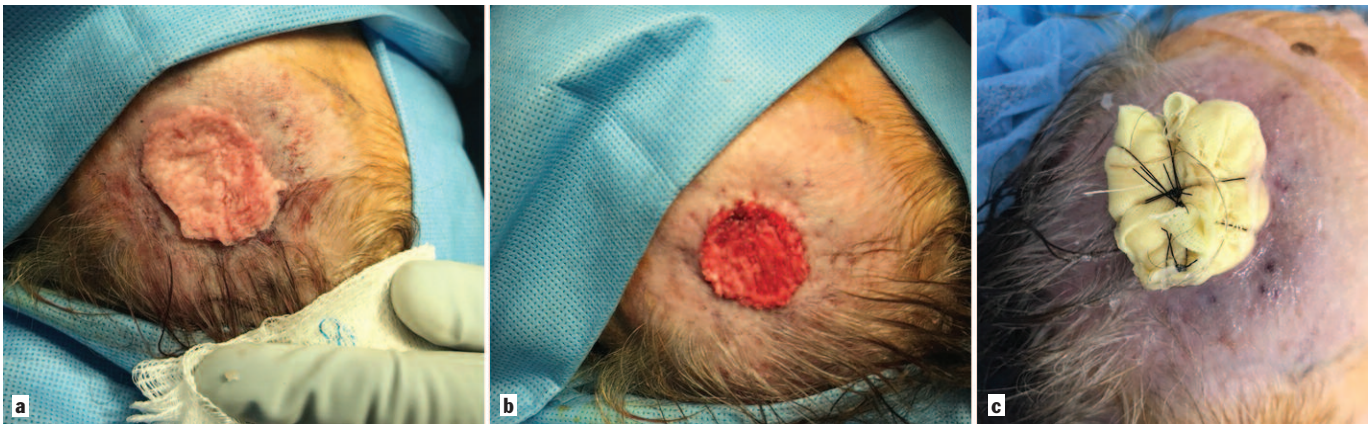


Figure 3. (a) Graft is applied and hydrated. (b) Graft immediately uptakes blood elements from wound. (c) Secured with monofilament absorbable suture and bolster dressing created and tied.

gauze was applied over the ECM tissue device graft. The bolster is secured and anchored with nylon sutures. The secured bolster dressing covers the ECM device and applies pressure to the graft holding it in place and to ensure contact of the ECM tissue device graft to the base of the wound defect (Fig. 4).

Full thickness excision of the basal cell skin cancer is achieved. Attention to removing the tumor with adequate skin margins can be applied without modification to accommodate simple closure techniques (elliptical excision). Excision with intent on maintaining the resection margin to achieve complete excision is more the focus and avoids taking extra skin and tissue in anticipation of closure. Given the planned use of an ECM device to fill the defect, deep margin removal can be more complete as the ECM device has been shown to fill and cover vital structures with good results.[14,15] Excision of deeper structures to bone or fascia can be performed with confidence that underlying structures will be covered at the conclusion of the operative procedure. In this manner complete excision of skin, Subcutaneous tissue and fascia exposing bone or other structures can be performed if required.[3]

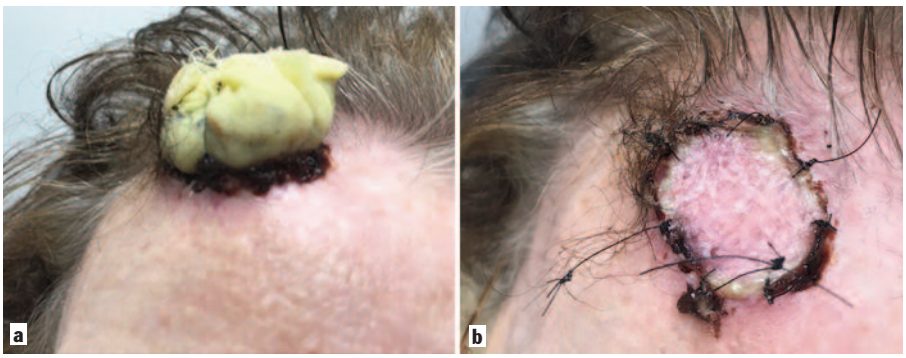


Figure 4. (a) 2-week follow-up visit. (b) Bolster is removed, graft is pink and becoming infiltrated with host cells.

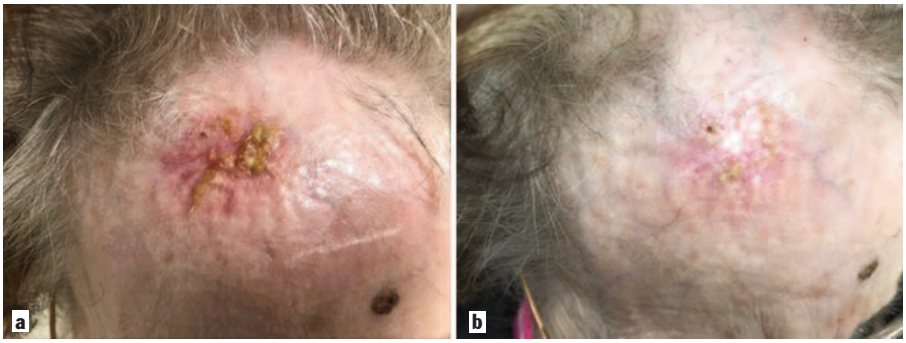


Figure 5. (a) Graft at 5 weeks. (b) Graft at 6 weeks. Healed and defect filled with little tissue loss deformity. Skin covered and level with surrounding skin.

In the event of a positive margin, planned re-excision specific to the involved quadrant can be performed. Directed re-excision results in less tissue removal that total re-excision. If a tissue deficit is created, additional ECM device can be applied to fill that defect without jeopardizing healing.

RESULTS

Patients are followed weekly. The bolster dressing is left in place for 2 weeks undisturbed. Antibiotic ointment is applied around the contact perimeter of the skin -bolster dressing. This helps to avoid drying of the ECM device. At 2 weeks, the dressing is removed and the graft material is examined. The ECM device is pink and looks viable as cellular infiltration has been initiated and occurred into the structure of the device (Fig. 5). Cellular signaling and remodeling of the ECM material is occurring. This remodeling of the ECM has been demonstrated to produce and result in factors that have major roles in healing. Degradation of the ECM releases multiple factors that play a role in orchestrating healing. Of these products, a group of leucine-rich proteoglycan factors are released. These molecules bind to growth factors and collagen affecting multiple essential cellular functions.[16-18] Cell differentiation, proliferation, and migration are but some of those functions. These processes affect collagen synthesis and scar formation. A specific factor, May-Day has been identified from remodeling of the provisional ovine ECM device that attracts endogenous mesenchymal stem cells to the device which may help further understand the role of a provisional matrix in wound healing.[16] Using a device to attract endogenous stem cells may help

explain the healed outcomes where by the excision site is repaired and seems to match well to surrounding tissues.[17] Evident in the excisions is that this type of secondary healing prompted by the ECM device allows the site to fill in avoiding the tissue deficit commonly seen in other techniques (Fig. 5).

DISCUSSION

Managing common skin cancers requires resection with negative margins in order to reduce the rate of recurrence.[1,2,5,7-11] Complete excision of skin cancer using this technique can proceed without undo concern over excising the lesion in an elliptical manner to accommodate for simple closure. The lesion is excised with emphasis on obtaining negative margins. Such a perimeter based excision leaves a tissue defect shape that traditionally has either been allowed to granulate, followed by skin grafting. Allowing the wound to granulate, particularly if the depth of the wound is periosteum or fascia can take a considerable amount of time. This delays grafting and time to a healed outcome. Negative pressure wound therapy (NPWT) can sometimes be used to help accelerate this process. NPWT however results in added therapy and the application of the mechanical device to the wound area. The matching of donor skin harvested to cover the defect can also be problematic as typically the graft donor skin fails to match the recipient area completely. Immediate skin grafting can result in a tissue deficit under the graft, and a noticeable deformity.

Local tissue flaps have been utilized to cover the defect but involves rearrangement of perimeter skin and tissue making margin identification more difficult in the event of a positive margin. Immediate flap closure has the disadvantage of changing the orientation of the margins. Should an involved margin be detected on pathology, deconstruction the flap and re-excision should be performed thus complicating subsequent closure.

Current xenograft extracellular matrix devices differ from previously available xenografts in that processing has been developed to preserve the bioavailability of active elements in the material. First, more diverse and biologically active tissues are used in the development of these devices in order that these factors are present in the material sufficient to provide these molecules in the end product provisional matrix.[16-18] In doing so, new modern day xenografts become incorporated and remodeled in the wound rather than immunologically rejected by the host. The matrix becomes a provisional structural extracellular matrix that will serve as a substrate for orchestrated healing. The matrix becomes actively remodeled and an active part of the process and in a fashion, consumed in healing rather than rejected. The basement membrane of the sheep foregut is used to produce the Myriad™ ECM device (Aroa Biosurgery). This highly active source tissue is rich in the components known to be involved in the healing process.[19] The ECM device has key elements known to impact and direct healing processes. New processing techniques are intended to maintain these bioactive properties of the material that are key to its effectiveness in orchestrating healing.[15,20] The retention of growth factors and other key molecules such as fibroblast growth factor, glycosaminoglycans (GAGS), fibronectin, hyaluronic acid, and laminin are important in healing.[19] The ECM device promotes granulation tissue formation in the wound providing structure for remodeling filling the defect.[16] With the ECM architectural structure intact, structural ligands are present that when fibroblasts attach to the ECM through these ligands, that interaction signals intracellular phenotypic programed change bringing about new sequenced cellular functions in fibroblasts. These new next step processes allow orderly healing and tissue remodeling to continue. Healing is further enhanced by the recruitment of stem cells to the surgical site.[16] The recent discovery of ECM-derived bioactive homing factors such as the May-Day protein attract stem cells to the site as the provisional matrix is remodeled by macrophages.[16] Attracting stem cells to the site through homing lends support to the effectiveness of these materials to impact on healing.[16]

The surgical excision site defects heal quickly and with minimal deformity and acceptable cosmetic results. The ECM tissue device graft does generate granulation tissue in the excision site. The granulated excision site does epithelialize with nearby cells which may ultimately better match surrounding skin as seen in the figures provided. Using an ECM device such as Myriad™ (Aroa Biosurgery) has advantages over immediate closure with flap or skin graft techniques by allowing permanent section evaluation of the margins of resection. In the event a positive margin is determined on permanent section, the specific quadrant can be resected and examined specific to that portion without significant disruption of the healing site. More directed re-excision can be undertaken avoiding disruption to the graft area. Once granulated, the site can be skin grafted if need be or in the case of appropriately sized sites, allowed to heal and epithelialize.[4,15] We have found that the healed result provides for acceptable cosmetic result and match to surrounding skin. Further development of ECM devices will bring about opportunities for use in surgical application. The healing potential of an ECM device that can actively participate in normal physiological processes opens new opportunities to re-examine even common surgical procedures as excisional treatment of common skin cancers.

CONCLUSION

Through continued healing research, a better understanding of the role a provisional ECM device has provided new opportunities to rethink typical approaches to surgical procedures. Biologically active devices are more commonly used in surgical procedures as an implant or adjunct. As the interactions orchestrated by the structural elements and peptides of an ECM are being better described, their application during surgery may well lead to improved healing outcomes.[21] This manuscript reports a new approach to common skin excisions where margin control is primarily important to the ultimate outcome. With the use of a provisional ECM matrix, attention to initial margin control can be more generous in terms of excision. Additionally, the use of an ECM device allows re-excision of an involved margin without the concern of disturbing a skin graft of more complex flap closure. STI

ACKNOWLEDGEMENTS

The author is grateful for the support of Aroa Biosurgery in expanding the application of healing science in surgery and translating into surgical procedures.

AUTHORS' DISCLOSURES

Dr. Bohn is a Medical Consultant for Aroa Biosurgery Ltd (Auckland, New Zealand).

REFERENCES

1. Work Group; Invited Reviewers, Kim JYS, et al. Guidelines of care for the management of basal cell carcinoma. J Am Acad Dermatol 2018;78(3):540-59.
2. Mehta KS, Mahajan VK, Chauhan PS, et al. Metastatic basal cell carcinoma: a biological continuum of basal cell carcinoma? Case Rep Dermatol Med 2012;2012: 157187.
3. Wain RA, Tehrani H. Reconstructive outcomes of Mohs surgery compared with conventional excision: A 13-month prospective study. J Plast Reconstr Aesthet Surg 2015;68(7):946-52.
4. Granick MS, Baetz NW, Labroo P, et al. In vivo expansion and regeneration of full-thickness functional skin with an autologous homologous skin construct: Clinical proof of concept for chronic wound healing. Int Wound J 2019;16(3):841-6.
5. Wetzig T, Woitek M, Eichhorn K, et al. Surgical excision of basal cell carcinoma with complete margin control: outcome at 5-year follow-up. Dermatology 2010;220(4):363-9.
6. Dawn ME, Dawn AG, Miller SJ. Mohs surgery for the treatment of melanoma in situ. Dermatol Surg 2007 Apr;33(4):395-402.
7. Goldberg DP. Assessment and surgical treatment of basal cell skin cancer. Clin Plast Surg 1997;24(4):673-86.
8. Griffiths RW, Suvarna SK, Stone J. Do basal cell carcinomas recur after complete conventional surgical excision? Br J Plast Surg 2005;58(6):795-805.
9. Ho C, Argáez C. Mohs Surgery for the Treatment of Skin Cancer: A Review of Guidelines. Ottawa, Ontario: Canadian Agency for Drugs and Technologies in Health. https://www.ncbi.nlm.nih.gov/books/ NBK546997/ March 20, 2019. Accessed November 30, 2020.
10. Sarnoff DS. Mohs Surgery: Still the Gold Standard - Sometimes too Much of a Good Thing. The Skin Cancer Foundation. https://www.carcinomasandkeratoses.org/2019-vol-1-2-mohs-surgery/ Accessed September 30, 2020.
11. Dim-Jamora KC, Perone JB. Management of cutaneous tumors with Mohs micrographic surgery. Semin Plast Surg 2008;22(4):247-56.
12. Nagi C, O'Grady TC, Izadpanah A. Mohs micrographically controlled surgery and the treatment of malignant melanoma. Semin Oncol 2002;29(4):336-40.
13. Finley EM. The Principles of Mohs Micrographic Surgery for Cutaneous Neoplasia. Ochsner J 2003 Spring; 5(2): 22-33.
14. Simcock J, May BC. Ovine forestomach matrix as a substrate for single-stage split-thickness graft reconstruction. Eplasty 2013;13:e58.
15. Chaffin AE, Bohn G. Clinical Evaluation of an Extracellular Matrix Surgical Graft for Reconstructive Surgery over Exposed Bone or Tendon. Symposium for Advanced Wound Care - Fall, Las Vegas, NV. 2019.
16. Dempsey SG, Miller CH, Schueler J, et al. A novel chemotactic factor derived from the extracellular matrix protein decorin recruits mesenchymal stromal cells in vitro and in vivo. 2020;PLoS ONE 15(7): e0235784.
17. Bohn G, Liden B, Schultz G, et al. Ovine-based collagen matrix dressing: Next-generation collagen dressing for wound care. Adv Wound Care (New Rochelle) 2016;5(1):1-10.
18. Irvine SM, Cayzer J, Todd EM, et al. Quantification of in vitro and in vivo angiogenesis stimulated by ovine forestomach matrix biomaterial. Biomaterials 2011;32(27):6351-61.
19. Dempsey SG, Miller CH, Hill RC, et al. Functional Insights from the Proteomic Inventory of Ovine Forestomach Matrix. J Proteome Res 2019;18(4): 1657-68.
20. Lun S, Irvine SM, Johnson KD, et al. A functional extracellular matrix biomaterial derived from ovine forestomach. Biomaterials 2010;31(16):4517-29.
21. Bohn GA, Schultz GS, Liden BA, et al. Proactive and Early Aggressive Wound Management: A Shift in Strategy Developed by a Consensus Panel Examining the Current Science, Prevention, and Management of Acute and Chronic Wounds. Wounds 2017 Nov; 29(11):S37-S42.

Extracellular matrix graft for reconstruction over exposed structures: a pilot case series

Objective: Soft tissue defects, especially those involving exposed vital structures, present a reconstructive challenge because poor vascularity of such defects typically makes immediate skin grafting unviable. Where flap procedures are inappropriate or not possible, dermal matrices represent an alternative reconstructive option for defects with denuded vital structures. With dermal matrices becoming increasingly available and technologically advanced, we evaluated an ovine-derived extracellular matrix graft in the reconstruction of complex soft tissue defects involving exposed vital structures.
Method: Six cases of soft tissue defects exhibiting denuded vital structures underwent reconstruction using an ovine forestomach matrix graft as a dermal matrix. Grafts were fixed directly into defects for immediate coverage and subsequently temporised defects via granulation tissue formation for later skin graft or secondary closure. Defect granulation and epithelialisation were monitored until closure and the final aesthetic and functional outcomes were evaluated.
Results: Complete healing was achieved in all cases, with defect granulation becoming observable within one to two weeks and complete granulation occurring within one to six weeks. Granulation tissue resulting from the graft was suitable for skin grafting, with 100% take of skin grafts after one week and complete re-epithelialisation in two to three weeks in the four cases that received a skin graft. Good cosmetic, functional and patient satisfaction outcomes were achieved in all cases.
Conclusion: The present series demonstrates our initial use of an extracellular matrix-based dermal matrix in reconstructing defects with exposed vital structures. While such dermal matrices do not supersede or replace flap procedures, they represent an alternative option on the reconstructive ladder in cases where flap procedures are not appropriate or possible.
Declaration of interest: The graft (Myriad Soft Tissue Matrix) was provided by Aroa Biosurgery Limited (Auckland, New Zealand). AEC and GAB have received educational travel grants from Aroa Biosurgery Limited.

dermal matrix • diabetes • dressing • exposed bone and tendon • extracellular matrix • ovine forestomach matrix • reconstructive surgery • wound

Reconstruction of defects presenting denuded vital structures is challenging. Exposed vessels, nerves, tendons, joints and bone must be promptly covered but immediate closure via a split-thickness skin graft (STSG) is not always a viable option. If not covered with adequately perfused soft tissue, exposed vital structures are at high risk of desiccation, necrosis and/or infection, posing severe functional consequences.[1] As exposed vital structures often have insufficient vascularisation to support an STSG, more complex surgical techniques from the reconstructive ladder are required.[2] Flap reconstruction is typically employed for coverage of exposed structures and to provide definitive closure. Depending on the nature of the defect and surrounding tissues, flap reconstruction options can range from relatively straightforward fasciocutaneous flaps to free flaps requiring more complex microvascular surgery. Flap techniques are recognised as reliable options for reconstruction of complex defects but, depending on the specific defect, flap type and patient factors, flap reconstruction may be complicated by dehiscence, infection, thrombosis, seroma/haematoma, ischaemia and necrosis.[3] Such complications require medical intervention to stabilise compromised flaps and additional surgery may be necessary to attempt salvage because flap failure has severe impacts on the reconstructive outcomes.

Dermal matrices (also called 'dermal substitutes' or 'dermal templates') are biomaterials typically comprised of collagen and/or other extracellular matrix (ECM) components. These devices are designed to act as biomimetic substitutes for soft tissue ECM and scaffold soft tissue regeneration prior to STSG placement or closure via secondary intention.[4,5] A range of dermal matrices are now commercially available, from products synthetically formulated using reconstituted collagen and other ECM components (e.g., Integra (Integra LifeSciences Corporation) and Matriderm (MedSkin Solutions Dr. Suwelack AG)) to decellularised ECM xenografts (e.g., Surgimend (Integra LifeSciences Corporation)) and allografts (e.g., Alloderm (Allergan plc)) that consist of purified tissue ECM.

Gregory A Bohn,[1] MD, Associate Professor of Surgery; **Abigail E Chaffin**,[2] MD, FACS, CWSP, FAPWCA, Associate Professor of Surgery and Program Director*
***Corresponding author email:** achaffin@tulane.edu
1 Department of Surgery, Central Michigan School of Medicine, St. Joseph Hospital, 200 Hemlock Rd, Tawas City, Michigan 48763, US. **2** Department of Surgery, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, Louisiana 70112, US.

Ovine forestomach matrix (OFM) is a decellularised xenograft ECM biomaterial composed of over 150 matrisome proteins,[6] and an open porous architecture to support cell infiltration.[7–10] OFM is manufactured from ovine forestomach using processes to remove the ovine cells, while retaining the architecture and composition of the tissue ECM. Clinically, OFM-based devices have been used in hard-to-heal wound management, plastics and general surgery.[11–14] More recently, OFM has been fabricated into multilayered grafts, called 'Myriad Soft Tissue Matrix', designed specifically for use as a dermal matrix in deep partial or full thickness defect reconstruction, as well as implant procedures. In the present case series, we describe our initial experiences using the OFM graft as a dermal matrix in the reconstruction of defects with exposed vital structures.

Methods

The retrospective case series was conducted in accordance with institutional guidelines conforming to the Declaration of Helsinki and informed written consent was obtained from patients. All patient information, including images were de-identified. This retrospective case series included five participants with six complex defects involving exposed structures (Table 1). The reconstructive procedures were conducted between 2018–2020 at two sites (New Orleans, Louisiana and Tawas City, Michigan). Where required, defects underwent aggressive sharp debridement to remove non-viable tissues, or full thickness excision. The OFM grafts (Myriad Soft Tissue Matrix, Aroa Biosurgery, Auckland, New Zealand) are engineered as multilayered devices comprising either 3-layer ('thin') or 5-layer ('thick') OFM bioscaffold. Devices are shelf stable at room temperature and were terminally sterilised. Graft thickness was selected by the surgeon based on the depth of the defect, then the grafts trimmed to fit the defect, rehydrated using sterile saline and placed in the defect, ensuring direct contact with the underlying tissues. Grafts were secured via suture or staple fixation and covered with a non-adherent contact layer. The OFM graft was applied only during the initial surgical procedure. Defects were regularly assessed for progress of graft incorporation and granulation tissue formation. When sufficiently granulated, STSGs were applied, apart from a single case of secondary closure (Case 2), and where the OFM graft was implanted (Case 6, Table 1). Regular assessment of STSG viability and defect epithelialisation was performed until complete healing, and the cosmetic and functional reconstructive outcomes evaluated.

Results

During preparation, both 'thick' (~1.5mm) and 'thin' (~1mm) OFM grafts were easily trimmed to fit the defect area and on hydration had excellent handling properties and mechanical strength. The OFM grafts notably

Table 1. Study participants

Case: Participant (sex, age)	Comorbidities	Defect type	Defect exposed structures	Previous management	Surgical management	Results
1 (F, 25)	Uncontrolled diabetes	Traumatic compression injury resulting in tissue ischaemia	Radial and ulnar arteries	Fasciectomies and debridements	OFM graft, NPWT, STSG	Complete granulation at 6 weeks; 100% skin graft take at 1 week; 100% epithelialisation at 9 weeks
2 (F, 25)	Uncontrolled diabetes	Secondary defect following z-plasty	Tendon	NA	Z-plasty scar revision, OFM graft, STSG	100% epithelialised after 4 weeks; elbow flexion improved from ~110° to 180°
3 (F, 98)	None, otherwise healthy	Full thickness tumour excision, scalp	Periosteum	None	OFM graft	Complete granulation in 2 weeks; closure by secondary intention after 8 weeks with good cosmetic outcomes
4 (M, 85)	Osteomyelitis	Non-healing surgical defect, scalp	Calvarium	Amniotic membrane graft (Epifix, MiMedx)	Full thickness excision, OFM graft, STSG	Complete granulation in 2 weeks; 100% epithelialised after 7 weeks
5 (F, 3)	Malnourished, pterygium syndrome	Surgical dehiscence; full-thickness hard-to-heal wound foot dorsum and calcaneus	Bone and tendon	Dermal substitute graft (Integra, Integra LifeSciences Corp)	OFM graft, STSG	Complete granulation in 1 week; 100% epithelialised in 2 weeks; long-term (3 months) improvements in function with 80% original ankle flexion restored
6 (M, 70)	Multiple comorbidities; complex ventral hernia after urologic cancer resection	Surgical dehiscence; non-healing abdominal sinus tract, adjacent to granulated bowel	Bowel	Wound debridement and NPWT	OFM graft implanted into tracking sinus, then STSG	Sinus tract closed at 3 weeks; STSG graft placed at 6 weeks; 100% epithelialised in 11 weeks

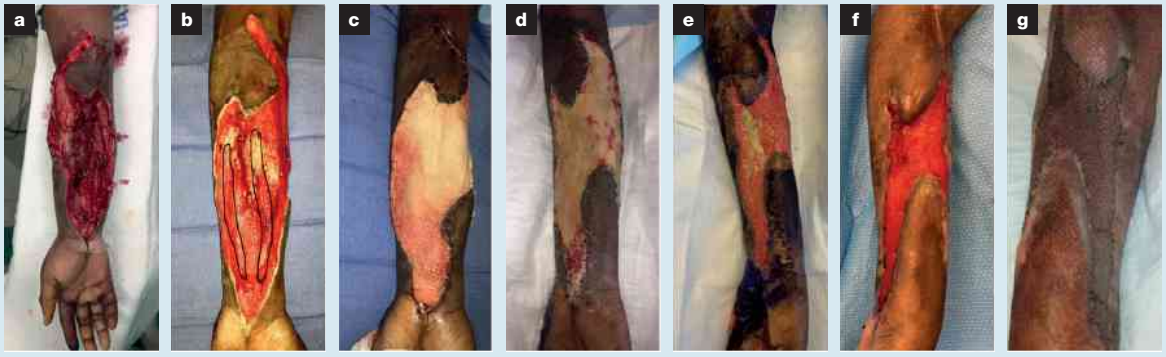
F—female; M—male; NA—not applicable; NPWT—negative pressure wound therapy; OFM—ovine forestomaach matrix; STSG—split-thickness skin graft

absorbed blood and blood components following placement. The availability of two graft thicknesses was useful when addressing the various depths seen in the defects managed, and avoided the need to layer multiple devices in the same defect. Fixation of the OFM graft via sutures or staples was straightforward, durably securing the graft to maintain contact with the underlying tissues and providing immediate coverage of exposed structures. Across all cases, initial signs of granulation tissue within the OFM graft appeared one to two weeks post application. Granulation tissue typically originated at the basal portion of the graft as small projections at the graft interstices that later merged into islands of granulation tissue. Defects were sufficiently granulated to receive an STSG within one to six weeks post application. As expected, larger defects required more time to completely granulate. Granulation tissue resulting from the OFM graft was well vascularised and a suitable substrate for an STSG. Where an STSG was used, 100% take of the STSG within one week was achieved and all defects were 100% re-epithelialised in two to three weeks. All defects healed with no complications, and no signs of infection were observed. All defects healed with good functional and cosmetic outcomes and patients reported high levels of satisfaction.

Case 1

A 25-year-old female patient with diabetes had been found down on her left arm for approximately 48 hours with diabetic ketoacidosis. Multiple fasciotomies and surgical debridements were required for the areas of necrotic tissue (Fig 1a). Soft tissue debridement was performed over one week, leaving radial and ulnar arteries visibly pulsatile and essentially exposed (Fig 1b) with debridement causing one artery to require arterial stitch repair. Soft tissue coverage was required to prevent arterial blowout. However, a large free flap procedure was not appropriate, given the patient's uncontrolled diabetes (HbA1c 14%), the risk of sacrificing another region to undertake a free flap and uncertainty of the future functional status of the arm. The patient refused below-elbow amputation recommended by the surgical team. Partial complex closure at the antecubital fossa and wrist was performed. Given the limited surgical options, the OFM graft was employed to provide immediate coverage and build granulation tissue in the defect. Due to the large defect size, two OFM grafts ('thick' 10×20cm and 'thick' 10×10cm) were quilted together with 4-0 chromic catgut suture, trimmed to fit the defect, hydrated in saline and placed in the defect with staple fixation (Fig 1c). A non-adherent dressing (Adaptic, Acelity Inc, San Antonio, Texas) was placed over the OFM graft, followed by a high-density negative pressure wound therapy (NPWT) foam dressing (V.A.C. WHITEFOAM, KCI Inc, San Antonio, Texas) and finally a low-density NPWT foam dressing (V.A.C. GRANUFOAM, KCI Inc). Continuous NPWT was performed at low pressure (75mmHg) due to the exposed arteries, with dressing changes twice per week. After four days, granulation tissue was visible in OFM graft interstices and in two weeks islands of granulation tissue were prominent throughout the graft and the distal graft portion was predominately robust granulation tissue (Fig 1d). Residual graft was debrided from the distal area and silver nitrate applied to mitigate hypergranulation. At this stage NPWT was ceased due to neuropathic pain at the periwound area, attributed to the extent of ischaemic neurologic injury. Hydrogel was applied to maintain a moist environment and the non-adherent dressing changed to an antimicrobial variant (Xeroform, Covidien, Dublin, Ireland). At three weeks granulation trajectory was well established, with the majority of the OFM graft resorbed into developing granulation tissue. After four weeks, only the mid volar forearm had residual OFM graft remaining and healthy granulation tissue was established throughout the rest of the defect (Fig 1e). Curette debridement was performed and dressing regimen maintained, resulting in complete granulation at six weeks (Fig 1f). An STSG

Fig 1. Traumatic wound of left arm with exposed vasculature (Case 1). Day 0, initial defect (**a**); Week 1, during debridement with exposed arteries outlined (**b**); Week 1, ovine forestomach matrix (OFM) graft placed (**c**); Week 2, formation of granulation islands in OFM graft (**d**); Week 4, defect near complete granulation with only small region of residual OFM graft remaining (**e**); Week 6, complete OFM graft incorporation and defect fully granulated (**f**); Week 7, 100% split-thickness skin graft take one week after placement (**g**)



(108cm^2, 0.3mm thick) was harvested and placed on the granulated defect, dressed with a silver contact layer (SilverIon) and NPWT applied for one week, resulting in 100% graft take (Fig 1g). Physiotherapy was initiated two weeks post STSG (eight weeks post initial intervention) and three weeks post STSG (nine weeks post initial intervention) and 100% defect epithelialisation was achieved, with functional improvements in wrist flexion and finger movement. Considering the initial circumstances of the injury and high risk of amputation, the patient was overwhelmingly pleased with the functional and cosmetic outcomes achieved.

Case 2

The same 25-year-old female patient (Case 1) underwent planned scar revision to release flexion crease, with revision surgery taking place one week after complete epithelialisation of the initial defect described above (four weeks post STSG and ten weeks post initial intervention). Scar contracture below the elbow (Fig 2a) was released via excision and the crucial flexion crease region reconstructed with local tissue by Z-plasty. Due to the significant prior ischaemic injury, release of deep scar tissue distal to the elbow created a secondary defect (Fig 2b). An OFM graft ('thin' 10×10cm) was trimmed to fit and placed in the defect (Fig 2c) secured via suture and conventional bolster and split. Two weeks post Z-plasty, scar release resulted in flexion improvement (from ~110° to ~180°) and the secondary defect was fully granulated (Fig 2d). An STSG was placed with complete graft take in one week and 100% epithelialisation two weeks post STSG placement (four weeks post scar revision) (Fig 2e).

Case 3

A 98-year-old female patient presented with Bowenoid squamous cell carcinoma in situ located on the forehead (Fig 3a). Initial tumour size was estimated to be ~1.5×1.5cm. Full-thickness excision of the tumour and margins down to periosteum was performed under general anaesthetic, creating a ~2.1×2.7cm defect (Fig 3b). Due to the defect location, depth and the patient's preference to avoid a donor-site wound, immediate coverage with an STSG was discounted. Instead, an OFM graft was used to provide coverage of the periosteum, and regenerate granulation tissue in the defect void, with closure via secondary healing. An OFM graft ('thick' 5×5cm) was trimmed, rehydrated in saline and placed to ensure good apposition to the underlying periosteum (Fig 3c). The graft was secured with 4-0 chromic suture and a bolster dressing of mineral oil, cotton balls and petrolatum dressing (Xeroform) with tie over silk suture compression. Two weeks post surgery, the OFM graft was integrating, and becoming vascularised with some residual graft visible (Fig 3d). After six weeks, 80% of the defect had re-epithelialised (Fig 3e), and the defect fully healed at eight weeks (Fig 3f). The patient was very satisfied with the cosmetic outcome achieved without the need for an STSG.

Case 4

An 85-year-old male patient with numerous prior scalp skin cancers presented with a two-year-old non-healing wound on the scalp vertex resulting from prior Mohs excision of squamous cell carcinoma (Fig 4a). Tissue surrounding the defect was abnormal and the defect had a history of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus lugdunensis* infection, with outer table calvarial osteomyelitis confirmed by MRI. Previous treatment of the defect with amniotic membrane allograft (Epifix, MiMedx, Marietta, Georgia) was unsuccessful, likely due to the underlying osteomyelitis and the chronicity of the dermal tissues. Full-thickness excision of the defect and surrounding

Fig 2. Z-plasty scar revision of left arm (Case 2). Day 0, initial presentation with incision plan marked (**a**); Day 0, post-z-plasty showing secondary defect in profile (top) and top-down (bottom) perspectives (**b**); Day 0, placement of ovine forestomach matrix graft in secondary defect depicted in profile (top) and top-down (bottom) perspectives (**c**); Week 2, secondary defect fully granulated (**d**); Week 4, secondary defect (circled) fully epithelialised two-weeks after split-thickness skin graft placement (**e**)

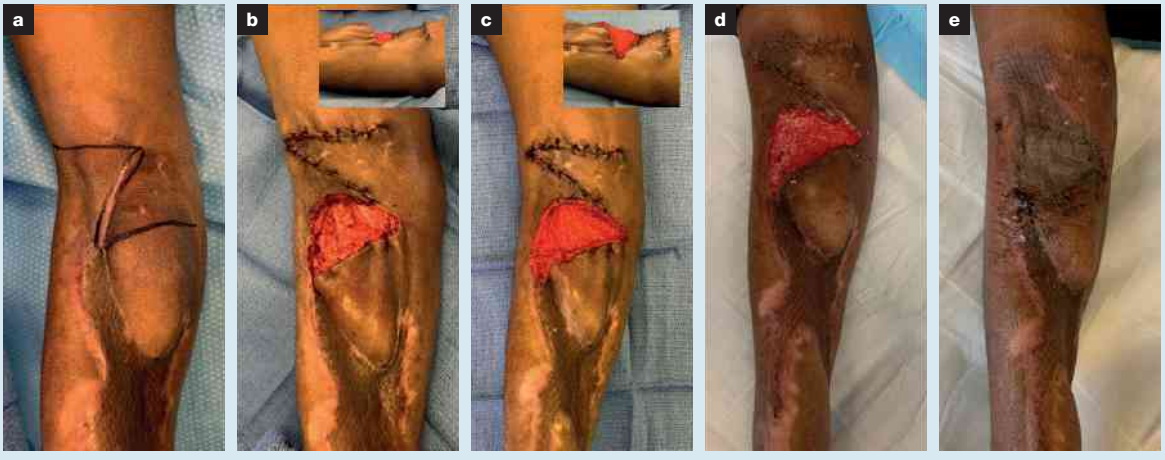
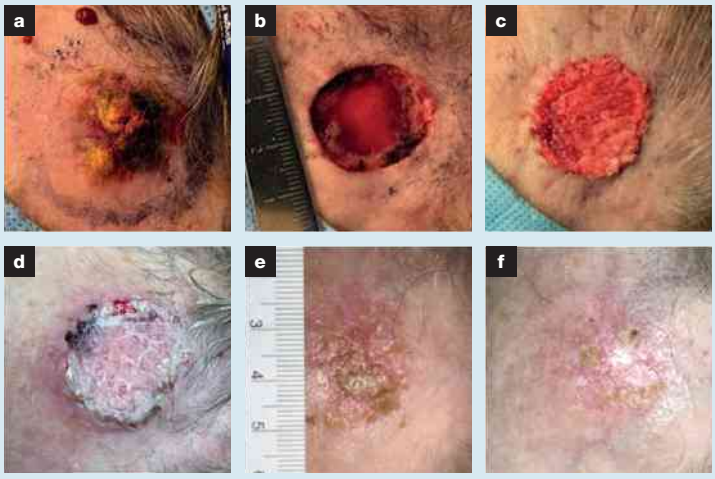


Fig 3. Scalp tumour excision defect (Case 3). Day 0, initial carcinoma (**a**); Day 0, surgical defect created follow tumour excision (**b**); Day 0, ovine forestomach matrix (OFM) graft placement (**c**); Week 2, OFM graft integrating with some residual graft visible (**d**); Week 6, 80% re-epithelialisation of defect via secondary intention (**e**); Week 8, complete secondary closure of defect (**f**)



abnormal scalp region was performed, irregular central calvarial bone consistent with osteomyelitis found and the outer table was debrided with a pineapple burr to punctate bleeding. The resulting defect measured 7.0×6.5cm with the calvarium not intact (Fig 4b). An OFM graft ('thick' 10×10cm) was cut to fit, rehydrated in saline and placed directly contacting the exposed bone, secured to defect edges with 4-0 chromic suture (Fig 4c) and compression via silk suture tie over bolster dressing (Fig 4d). After two weeks, granulation tissue was observed within the graft material (Fig 4e) and the outer (top) graft layer removed via gentle traction revealing complete incorporation of the inner graft layers into newly formed granulation tissue (Fig 4f) and no signs of infection within the defect area. At four weeks post initial surgery, an STSG (0.3mm thick) was applied (Fig 4g) and 100% graft take achieved one week after placement. Three weeks after STSG placement (seven weeks post initial surgery) the defect had completely epithelialised (Fig 4h), with the healed area demonstrating good contour, colouration and functional elasticity.

Case 5

A 3-year-old female patient with pterygium syndrome underwent an orthopaedic procedure of the left foot resulting in wound dehiscence and infection. The patient was admitted malnourished and presented a full-thickness tissue deficit with exposed bone and tendon (Fig 5a). Previous treatment using a reconstituted collagen/glycosaminoglycan dermal matrix (Integra) was unsuccessful. Due to the defect location, flap reconstruction was ruled out by the surgical team. The defect was debrided and an OFM graft ('thick' 10×20cm) was placed, conforming to the defect bed and covering the exposed bone and tendon. The graft was secured via staples at the margins (Fig 5b) and covered with a non-adherent layer (SilverIon, Argentum Medical, Geneva, Illinois), silver alginate dressing for moisture retention and finally cast padding wrap and split. At one-week follow-up, graft incorporation was apparent with granulation tissue visible through the graft material (Fig 5c). The extent of granulation tissue was sufficient for STSG placement (0.3mm thick). Complete STSG take to the neodermis was observed one week post STSG placement (two weeks post initial OFM graft placement) (Fig 5d). At long-term follow-up, three months post STSG placement, movement of the joint had nearly returned to pre-operation status, with only ~20% loss of ankle flexion, and regenerated dermis demonstrated good cosmesis and functional elasticity (Fig 5e).

Discussion

Exposed vital structures in soft tissue defects require prompt and durable stabilisation during reconstruction to protect and maintain vitality up to definitive closure. Defects with exposed vital structures often lack the vascular supply required to reliably support direct STSG placement. Thus, gold standard treatment is coverage by a well vascularised flap that can sustain and protect the exposed structures, while providing immediate coverage. However, the use of flap-based reconstruction may be limited by donor site morbidity concerns, the absence of sufficient donor tissue or a lack of subspecialty training.[2]

Scientific research has continued to advance our understanding of tissue ECM and in parallel the development of regenerative bioscaffolds, like dermal matrices, that aim to mimic tissue ECM to scaffold soft tissue regeneration.[15] Correspondingly, the traditional reconstructive ladder has evolved to include dermal matrices as an additional option for surgically managing complex soft tissue defects.[16,17] The objectives of treating defects with denuded vital structures with dermal matrices is to provide an initial protective coverage to exposed structures, then temporise the defect via scaffolding granulation tissue formation. Once granulation tissue has been regenerated, closure may be achieved via skin grafting or closure via secondary intention. Reflecting their uptake in clinical practice, the use of dermal matrices in reconstruction involving exposed structures has been reported widely.[1,18–20]

A variety of dermal matrices are now commercially available, including synthetic bioscaffolds and a range of decellularised ECM grafts derived from human and animal tissues.[15] Synthetic bioscaffolds use processes that synthesise bioscaffolds from component raw materials (e.g., synthetic polymers, reconstituted collagen, chondroitin sulphate or elastin) to create biomaterials of defined pore and fibre size. Decellularised ECM bioscaffolds represent a newer evolution in bioscaffold design, and rather than being synthetic, these products are produced using processes to isolate an intact tissue ECM from mammalian tissue sources. The tissue ECM

undergoes decellularisation to remove any cellular components from the raw tissue starting material, and retains the structure and composition of tissue ECM.[15]

In the treatment of defects with exposed vital structures, the most well characterised dermal matrix product is a synthetic product comprising reconstituted collagen crosslinked to chondroitin sulphate (Integra).[1,16,17,19] In comparison, the OFM graft consists of decellularised ECM and therefore has a significantly more diverse composition. For example, while also containing collagen and glycosaminoglycans,[7] a proteomic characterisation of the OFM biomaterial identified over 150 unique matrix proteins that naturally exist in soft tissue ECM and are known to play a role in soft tissue repair.[6] This includes a range of structural proteins, with 19 different collagens, adhesion proteins (e.g., fibronectin, tenascin) and signalling molecules such as growth factors (e.g., FGF2, PDGF, EGF and IGF), and inhibitory proteins (e.g., TIMP4).[6] Additionally, structural studies demonstrate that OFM retains a native matrix architecture similar to the ECM of healthy human skin.[9] This structural and compositional mimicry of healthy tissue ECM facilitates a range of biological properties, for example OFM to inhibit a range of tissue proteases,[21] and stimulate cell migration, infiltration, proliferation and differentiation,[7,8,22] and the recruitment of mesenchymal stromal cells.[10] In comparison to a synthetic dermal matrix, such as reconstituted collagen/glycosaminoglycan, the OFM graft is expected to impart greater biological functionality, attributed to a preserved ECM structure and composition.

In the present cases, we observed the OFM graft closely conformed to the defect bed and provided a durable protective layer to the defect and exposed vital structures. We noted that even when previously rehydrated in saline the OFM graft rapidly absorbed blood and blood components in situ, which may provide additional regenerative properties to the graft. In all cases we noted robust granulation tissue formation as the OFM graft integrated into the regenerating tissue. Our clinical observations are in agreement with previous reports demonstrating that the OFM biomaterial stimulated angiogenesis and vasculogenesis in vitro, ex vivo and in vivo.[8] Additionally, the physical design of the graft, including layers of OFM and regular interstitial perforations, appeared to guide cell infiltration and granulation tissue formation, with early granulation tissue observed in the graft interstices that later merged to distinct islands of granulation tissue. The availability of two thickness options (3-layer and 5-layer) allowed a graft to be selected to best suit the depth of the particular defect. However, the choice of graft thickness must take into consideration the entire reconstructive timeline, as graft thickness, as well as patient factors, will dictate the time to complete graft incorporation. Another procedural benefit of the OFM graft is the ability to implant the device to reinforce and rebuild subcutaneous soft tissues. For example, in Case 6 (Table 1), a non-healing abdominal sinus tract was packed with the OFM graft to close the tunnelled wound, thus preventing an enterocutaneous fistula forming in this patient. While the authors have considerable experience with reconstituted collagen/glycosaminoglycan grafts, the relatively high reported

Fig 4. Tumour excision with exposed bone and damaged calvarium (Case 4). Day 0, initial presentation of chronic defect and surrounding abnormal tissue (**a**); Day 0, full-thickness surgical defect after excision, calvaria not intact (**b**); Day 0, ovine forestomach matrix (OFM) graft applied to defect (**c**); Day 0, compression of OFM graft via bolster dressing (**d**); Week 2, granulation tissue formation within OFM graft with residual OFM graft present (**e**); Week 2, residual OFM graft removed, defect well granulated with no signs of infection (**f**); Week 4, split-thickness skin graft (STSG) applied to granulated defect (**g**); Week 7, completely epithelialised defect 3-weeks post STSG (**h**)

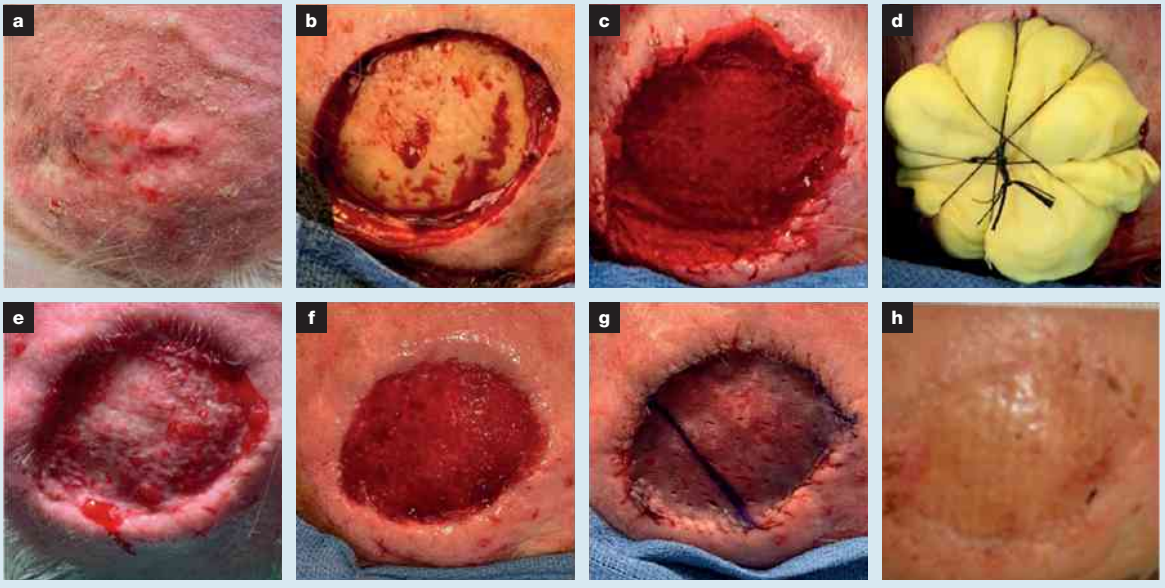
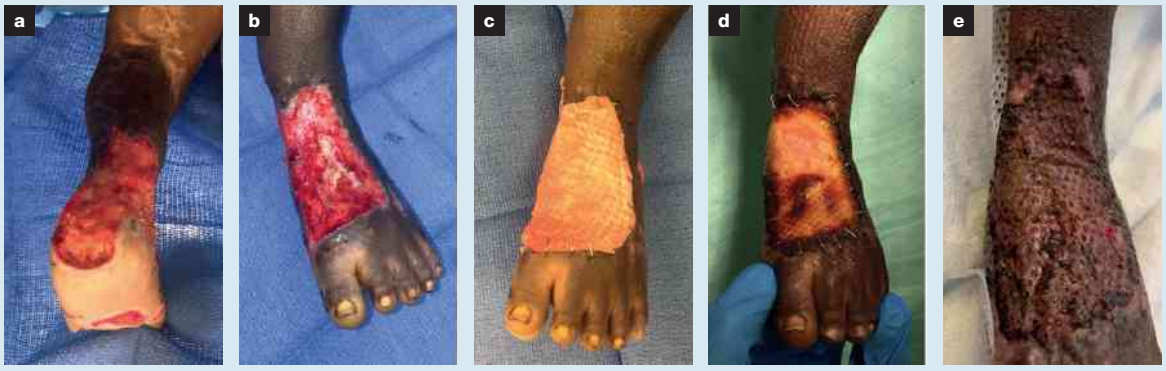


Fig 5. Paediatric wound dehiscence with exposed bone and tendon (Case 5). Proximal (**a**) and dorsal (**b**) aspect of full-thickness defects with exposed vital structures following surgical wound dehiscence and infection; Day 0, ovine forestomach matrix (OFM) graft placement (**c**); Week 1, granulation tissue visible within OFM graft and defect ready for skin grafting (**d**); Week 2, 100% STSG take one-week after split-thickness skin graft placement, dorsal perspective (**e**)



rates of infection[23–25] associated with this product raised concerns with using this graft in the presence of potential infection. No infections were observed in the use of the OFM graft, even in previously contaminated sites (Cases 4 and 5). While further studies are warranted to quantify infection rates using the OFM graft, it is interesting to speculate on the absence of infections seen in this pilot series. The biology and structure of the OFM bioscaffold have been shown to aid rapid vascularisation that may hinder microbial challenge through the delivery of immune components to the site. Additionally, it has been shown in previous studies that decellularised ECM bioscaffolds contain naturally occurring antimicrobial proteins that may also limit infection.[26]

Conclusion

When determining reconstructive strategy, the surgeon must consider specific defect and patient factors while also balancing procedural complexity, time and cost with the probability of best long-term aesthetic and functional outcomes for the patient. A number of strategies are available to the reconstructive surgeon and technological advances have provided new options on the reconstructive ladder for the treatment of soft tissue defects, such as the use of dermal matrices in the reconstruction of defects with denuded vital structures. Dermal matrices do not replace the need for established flap procedures, but these materials provide a range of additional options in the surgeon's repertoire to consider when determining the best reconstructive approach. The present work represents our initial clinical experience using an OFM graft and indicates the utility of this ECM-based dermal matrix in the reconstruction of challenging defects complicated by exposed vital structures. These cases support further controlled studies to assess the clinical performance, health economics and long-term outcomes of the OFM graft compared to other dermal matrices. **JWC**

Acknowledgements

The authors would like to acknowledge Aroa Biosurgery Limited (New Zealand) for assistance in the preparation of this manuscript.

References

1 Reynolds M, Kelly DA, Walker NJ et al. Use of Integra in the management of complex hand wounds from cancer resection and nonburn trauma. Hand (N Y) 2018; 13(1):74–79. https://doi.org/10.1177/1558944717692090

2 Boyce DE, Shokrollahi K. ABC of wound healing: reconstructive surgery. BMJ 2006; 332(7543):710–712. https://doi.org/10.1136/bmj.332.7543.710

3 Rubayi S. Complications of flap surgery. In: Reconstructive plastic surgery of pressure ulcers. Springer; 2015:243–248. https://doi.org/10.1007/978-3-662-45358-2_15

4 Brenner MJ, Moyer JS. Skin and composite grafting techniques in facial reconstruction for skin cancer. Facial Plast Surg Clin North Am 2017; 25(3):347–363. https://doi.org/10.1016/j.fsc.2017.03.007

5 Faulhaber J, Felcht M, Teerling G et al. Long-term results after reconstruction of full thickness scalp defects with a dermal regeneration template. J Eur Acad Dermatol Venereol 2010; 24(5):572–577. https://doi.org/10.1111/j.1468-3083.2009.03473.x

6 Dempsey SG, Miller CH, Hill RC et al. Functional Insights from the Proteomic Inventory of Ovine Forestomach Matrix. J Proteome Res 2019; 18(4):1657–1668. https://doi.org/10.1021/acs.jproteome.8b00908

7 Lun S, Irvine SM, Johnson KD et al. A functional extracellular matrix biomaterial derived from ovine forestomach. Biomaterials 2010; 31(16):4517–4529. https://doi.org/10.1016/j.biomaterials.2010.02.025

8 Irvine SM, Cayzer J, Todd EM et al. Quantification of in vitro and in vivo angiogenesis stimulated by ovine forestomach matrix biomaterial. Biomaterials 2011; 32(27):6351–6361. https://doi.org/10.1016/j.biomaterials.2011.05.040

9 Sizeland KH, Wells HC, Kelly SJ et al. Collagen fibril response to strain in scaffolds from ovine forestomach for tissue engineering. ACS Biomater Sci Eng 2017; 3(10):2550–2558. https://doi.org/10.1021/acsbiomaterials.7b00588

10 Dempsey SG, Miller CH, Schueler J et al. A novel chemotactic factor derived from the extracellular matrix protein decorin recruits mesenchymal stromal cells in vitro and in vivo. PLoS One 2020; 15(7):e0235784. https://doi.org/10.1371/journal.pone.0235784

11 Bohn GA, Schultz GS, Liden BA et al. Proactive and early aggressive wound management: a shift in strategy developed by a consensus panel examining the current science, prevention, and management of acute and chronic wounds. Wounds 2017; 29(11):S37–S42

12 Simcock J, May BC. Ovine forestomach matrix as a substrate for single-stage split-thickness graft reconstruction. Eplasty 2013; 13:e58

13 Ferzoco SJ. Early experience outcome of a reinforced bioscaffold in inguinal hernia repair: a case series. Int J Surg Open 2018; 12:9–11.

https://doi.org/10.1016/j.ijso.2018.06.001
14 Sawyer MA. New ovine polymer-reinforced bioscaffold in hiatal hernia repair. JSLS 2018; 22(4):e2018.00057. https://doi.org/10.4293/JSLS.2018.00057
15 Scarritt M, Murdock M, Badylak SF. Biologic scaffolds composed of extracellular matrix for regenerative medicine. In: Principles of regenerative medicine. Elsevier; 2019:613-626
16 Janis JE, Kwon RK, Attinger CE. The new reconstructive ladder: modifications to the traditional model. Plast Reconstr Surg 2011; 127(Suppl 1):205S–212S. https://doi.org/10.1097/PRS.0b013e318201271c
17 Goel P, Badash I, Gould DJ et al. Options for covering large soft tissue defects in the setting of trauma. Curr Trauma Rep 2018; 4(4):316–325. https://doi.org/10.1007/s40719-018-0146-y
18 Ellis CV, Kulber DA. Acellular dermal matrices in hand reconstruction. Plast Reconstr Surg 2012; 130(5 Suppl 2):256S-269S. https://doi.org/10.1097/PRS.0b013e318265a5cf
19 Graham GP, Helmer SD, Haan JM, Khandelwal A. The use of Integra Dermal Regeneration Template in the reconstruction of traumatic degloving injuries. J Burn Care Res 2013; 34(2):261–266. https://doi.org/10.1097/BCR.0b013e3182853eaf
20 Hoang D, Steven P, Chen VW et al. Use of acellular dermal matrix following fasciectomy for the treatment of Dupuytren's disease. Plast Reconstr Surg Glob Open 2019; 7(5):e2263. https://doi.org/10.1097/GOX.0000000000002263
21 Negron L, Lun S, May BC. Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. Int Wound J 2014; 11(4):392–397. https://doi.org/10.1111/j.1742-481X.2012.01106.x
22 Overbeck N, Nagvajara GM, Ferzoco S et al. In-vivo evaluation of a reinforced ovine biologic: a comparative study to available hernia mesh repair materials. Hernia 2020. https://doi.org/10.1007/s10029-019-02119-z
23 Nguyen DQ, Potokar TS, Price P. An objective long-term evaluation of Integra (a dermal skin substitute) and split thickness skin grafts, in acute burns and reconstructive surgery. Burns 2010; 36(1):23–28. https://doi.org/10.1016/j.burns.2009.07.011
24 Heimbach DM, Warden GD, Luterman A et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. J Burn Care Rehabil 2003; 24(1):42–48. https://doi.org/10.1097/00004630-200301000-00009
25 Peck MD, Kessler M, Meyer AA, Bonham Morris PA. A trial of the effectiveness of artificial dermis in the treatment of patients with burns greater than 45% total body surface area. J Trauma 2002; 52(5):971–978. https://doi.org/10.1097/00005373-200205000-00024
26 Sarikaya A, Record R, Wu CC et al. Antimicrobial activity associated with extracellular matrices. Tissue Eng 2002;8(1):63–71. https://doi.org/10.1089/107632702753503063

Reflective questions

- When managing extensive soft tissue loss with exposed bone or tendon, how often is immediate placement of a split thickness skin graft appropriate?
- A dermal substitute can be used to build granulation tissue over exposed bone but the formation of granulation tissue of can be rate limiting. Typically, how long does complete integration of a dermal substitute take?
- When using a dermal substitute as part of a staged procedure, how often does reconstruction become complicated by infection of the dermal substitute?

frontiers in Surgery

CASE REPORT
published: 26 January 2021
doi: 10.3389/fsurg.2020.559450

Case Report: Surgical Closure of Chronic Soft Tissue Defects Using Extracellular Matrix Graft Augmented Tissue Flaps

Micheal N. Desvigne[1,2]*, *Krista Bauer*[2], *Kurt Holifield*[2], *Kari Day*[2], *Denise Gilmore*[2] and *Ashley L. Wardman*[2]

[1] Desvigne Plastic Surgery, Scottsdale, AZ, United States, [2] Abrazo Arrowhead Hospital, Glendale, AZ, United States

Chronic soft tissue defects are notoriously difficult to heal. Surgical reconstruction of chronic defects using tissue flaps is a routine approach for closure of challenging chronic defects. Due to the poor tissue quality of chronic defects and associated inflammation, infection and impaired blood supply the success of flap closure is marred by reported complication rates of 25–58%. Extracellular matrix (ECM)-based graft materials are commonly used for resolving chronic wounds and in plastic and reconstructive procedures to create a scaffold for tissue regeneration. We hypothesized combination use of ECM grafts with tissue flaps in a single-stage surgical procedure would reduce complications and improve outcomes in the closure of chronic soft tissue defects. We report a case series ($n = 9$) of chronic soft tissue defect reconstruction using this modified procedure of ECM graft augmented flap closure. Defects included pressure injuries and surgical dehiscence and ranged in wound age from 5 months to 7 years. Successful uncomplicated healing was achieved in six defects. Post-operative complications (dehiscence) occurred in two defects, however, these healed *via* secondary intention without additional surgical intervention. All healed defects exhibited acceptable cosmesis and "normal" function, with 100% patient satisfaction. Augmentation of tissue flaps with ECM graft materials in this modified single-stage procedure may improve outcomes and minimize typical complications encountered in flap closure of chronic defects attributed to inflammation, infection, hypoperfusion, and dead space.

Keywords: flap reconstruction, chronic wounds, soft tissue defects, extracellular matrix, ovine forestomach matrix

OPEN ACCESS

Edited by:
Charles M. Malata, Anglia Ruskin University, United Kingdom

Reviewed by:
Oren Lapid, Amsterdam University Medical Center (UMC), Netherlands
Fatih Zor, Wake Forest School of Medicine, United States

***Correspondence:**
Micheal N. Desvigne
mdesvigne@desvignemd.com

Specialty section:
This article was submitted to Reconstructive and Plastic Surgery, a section of the journal Frontiers in Surgery

Received: *06 May 2020*
Accepted: *15 December 2020*
Published: *26 January 2021*

Citation:
Desvigne MN, Bauer K, Holifield K, Day K, Gilmore D and Wardman AL (2021) Case Report: Surgical Closure of Chronic Soft Tissue Defects Using Extracellular Matrix Graft Augmented Tissue Flaps. Front. Surg. 7:559450. doi: 10.3389/fsurg.2020.559450

INTRODUCTION

Flap reconstruction is a well-established approach to the closure of chronic soft tissue defects however, post-operative complications such as infection, dehiscence, and re-occurrence are relatively common. The long-term success of flap closure is further complicated by patient co-morbidities such as obesity, diabetes and venous insufficiency. Retrospective analysis of 755 pressure injuries managed *via* flap closure demonstrated an overall complication rate of 25% at 30-day follow up (1). A prospective study of 276 pressure injuries closed by flap advancement demonstrated a complication rate of 58%, where wound dehiscence (31.2%) and re-occurrence (28.6%) were the most frequent complications (2). These complications associated with flap closure

of chronic soft tissue defects are likely attributable to the poor quality of the underlying tissues which may be fibrotic and/or inflamed, the dead space potential between the advancing flap and underlying tissue, and poor vascularity of the tissues in general.

Extracellular matrix (ECM) grafts are absorbable bioscaffolds commonly used across a range of plastic and reconstructive procedures to scaffold soft tissue repair. These technologies provide a temporary scaffold for cellular infiltration and capillary formation while providing protective coverage and reinforcement of the defect until the bioscaffold is absorbed into the regenerating soft tissues (3). Many different ECM grafts are clinically available and differ in the origins of the source tissue (e.g., human, porcine, bovine, equine) and the processes used to decellularize the tissue to remove nuclear and cellular material while preserving the structure and composition of the tissue ECM.

Ovine forestomach matrix (OFM), is a decellularized ECM bioscaffold isolated from ovine forestomach tissue and has an established use in a range of clinical applications such as the management of acute and chronic wounds (4–9), skin grafting (10) and abdominal wall repair (11, 12). Previous studies have demonstrated OFM exerts a variety of biological functions. For example, OFM exhibits anti-inflammatory effects with broad-spectrum tissue protease modulation (13, 14), as well as stimulation of cell migration, differentiation and infiltration (15, 16). The matrix promotes neovascularization and is populated *via* cellular infiltration and completely remodeled into the regenerating tissues (16). Insights into the mechanisms behind these biological effects are provided by analysis of the structure and composition of OFM. To date, 151 different matrisomal proteins have been identified in the material that include a wide variety of collagens, adhesion proteins, and signaling molecules such as 12 growth factors including but not limited to fibroblast growth factor 2 (FGF2), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and connective tissue growth factor (CTGF) (15, 17). Structural studies have demonstrated that collagen fibril integrity and functional responses are preserved in OFM thus reflecting the retention of native ECM architecture (18). The material is highly porous and conducive to fluid imbibement and cellular infiltration, in addition to having robust mechanical properties suitable for incorporation into devices for load bearing indications (19).

Considering the regenerative properties of ECM grafts, it was hypothesized that complications following flap reconstruction of chronic wounds may be reduced by inclusion of an ECM graft to stabilize and augment the surgical flap and underlying tissues. This pilot case series presents our initial findings implementing this strategy.

MATERIALS AND METHODS

Retrospective data was collected from operation notes, clinical photography, and clinical records. A total of $n = 9$ defects from 9 patients were included in the case series (**Table 1**). All patients had various comorbidities known to complicate healing and were to undergo a planned flap reconstruction of a chronic defect. All defects were chronic and non-healing with an age range of 5 months to 7 years. All defects were prepared *via* sharp debridement or aggressive excision of chronic tissues. The OFM ECM graft (Myriad^{TM} Soft Tissue Matrix, Aroa Biosurgery Limited, Auckland, New Zealand), was rehydrated in sterile saline ($\sim$ 5 min), trimmed to size, then placed into the base of the defect. Defects were then closed by local flap advancement and 3-0 Monocryl suture. Jackson-Pratt (JP) drains and incisional negative-pressure wound therapy (NPWT) were used as required (**Table 1**). Defects were monitored for up to 3–6 months (**Table 1**) for dehiscence, infection or recurrence.

RESULTS AND CASE EXAMPLES

We hypothesized that the concurrent placement of an underlaid ECM graft during flap reconstruction of chronic wounds may reduce surgical complications by reducing inflammation of the proximal tissues and stabilizing the flap. Using this strategy, uncomplicated healing was achieved in $n = 7$ of the $n = 9$ study participants with defects (**Table 1**). Post-operative complication, namely dehiscence, occurred in $n = 2$ of the defects. However, both of these defects progressed to heal secondarily with no additional surgical intervention required. All healed defects demonstrated good cosmesis comparable to adjacent tissues. Assessment of healed defects demonstrated excellent functionality and motion and all patients were satisfied with their respective outcomes.

Case 1

Fifty-three-year-old obese male who had a single-port laparoscopic gastric band placement performed 10 years prior. The band eroded through the skin and was surgically removed but closure was complicated by secondary dehiscence. At the time of intervention, the patient had a non-healing abdominal wound for 11 months, a more recent revision surgery (5 months prior) had also failed with a dehisced surgical site. Previous management of the defect was carried out *via* alginate dressings, cadexmer iodine, and saline gauze. The defect was causing moderate pain, but was clean with no evidence of infection and hypertrophic granulation tissue was present (**Figure 1A**). Surgical incision was made at the defect margins, through subcutaneous adipose tissue and down to the fascia (**Figure 1B**). An ECM graft (Myriad^{TM}, "Thick") was trimmed to fit the defect and placed onto the fascia (**Figure 1C**). Due to the depth of the defect and potential for dead space, second and third layers of ECM graft were prepared and placed in the defect in a layered arrangement. The defect was then closed by flap advancement with subcutaneous running suture with JP drain placed and incisional NPWT initiated. After seven days, cutaneous tissues demonstrated good apposition and tissues exhibited no inflammation (**Figure 1D**), the NPWT and drain were removed and patient was discharged with instruction to wear abdominal binder and 6 weeks heavy lifting/strenuous activity restriction. At 6 months, the site remained closed with no dehiscence or other complications.

TABLE 1 | Participants.

Participant (years)	Type	Comorbidities	Wound age	Location	Previous management	Surgical management	Time of last follow-up
Male, 53 (Case 1)	Surgical dehiscence post gastric band revision	Obesity	5 months	Abdomen	Alginate, surgical closure, cadexomer-iodine, saline gauze	Excision, ∼8 × 2 cm defect, fasciocutaneous advancement flap, incisional NPWT, JP drain	Remained healed at 6 months
Female, 67	Surgical dehiscence post ileostomy	Diverticulitis, rheumatoid arthritis	48 months	Abdomen	NPWT	Excision, ∼8 × 3 cm defect, fasciocutaneous advancement flap, incisional NPWT, JP drain	Remained healed at 6 months
Female, 70	Stage 4 pressure injury	Multiple sclerosis, paraplegia	6 months	Sacral and gluteal	Saline gauze	Excision, ∼15 × 6 cm defect, fasciocutaneous rotation flap, incisional NPWT	Remained healed at 6 months
Female, 73 (Case 2)	Stage 4 pressure injury	Parkinson's disease, Lupus, rheumatoid arthritis	7 years	Sacral	Previous flap reconstruction failed 1 month prior. Collagenase debridement, medical honey	Excision, ∼8 × 4 cm defect, fasciocutaneous rotation flap, partial ostectomy, incisional NPWT	Postoperative dehiscence, Secondary healing at 3 months Remained healed at 6 months
Male, 62	Stage 4 pressure injury	Diabetes mellitus, paraplegia, Parkinson's disease, Lupus, rheumatoid arthritis	7 years	Sacral (×3)	Calcium alginate	Excision, ∼8 × 4 cm, ∼8 × 5 cm, and ∼7 × 7 cm defects, fasciocutaneous advancement flaps, partial ostectomy, incisional NPWT	Remained healed at 6 months
Female, 26 (Case 3)	Surgical wound following open reduction internal fixation	Smoker	13 months	Ankle	Calcium alginate, ECM	Excision, ∼8 × 8 cm defect, fasciocutaneous rotation flap, incisional NPWT	1 week—dehiscence with infection 11 weeks—wound healed Remained healed at 6 months
Female, 71	Surgical wound abdomen	Deep vein thrombosis, heart murmur, hypertension, diverticulitis, hyperthyroidism, obesity	5 months	Abdomen	Ca Alginate	Excision, ∼6 × 2 cm defect, fasciocutaneous advancement flap, complex closure	Remained healed at 6 months
Male, 58	Sebaceous cyst, neck with active punctum	Obesity	4 years	Neck	Previous Incision and drainage	Excision, ∼5 × 3 cm defect, fasciocutaneous advancement flap, complex closure	Remained healed at 3 months
Female, 64	Nodule excision	Previous breast cancer	12 months	Axilla	NA	Excision, ∼9 × 4 cm defect, fasciocutaneous advancement flap, complex closure	Remained healed at 6 months

Case 2

Seventy-three-year-old female who was non-ambulatory secondary to Parkinson's disease, Lupus, and rheumatoid arthritis. Sacral pressure injury had been present for 7 years and had been previously managed with medical honey and enzymatic debridement. The patient had undergone a reconstructive procedure 1 month prior, using excision of the defect and flap coverage. The flap had subsequently dehisced and while there were no signs of infection, the defect was chronically inflamed (**Figure 2A**). Defect was excised with side margins down to

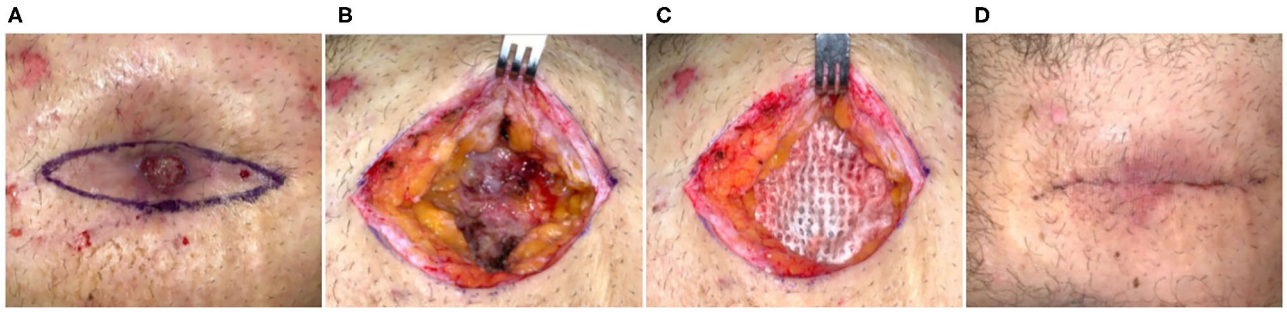


FIGURE 1 | Flap advancement and ECM stabilization of an abdominal dehiscence. Case 1—**(A)** Erosion of the abdominal tissues resulting from a gastric band and failed previous surgical reconstruction of the ∼11-month-old defect. **(B)** Wide excision of the defect down to the underlying fascia and adipose tissue. **(C)** Placement of the ECM graft into the base of the defect prior to flap advancement and closure. **(D)** Seven days post-op. Remained healed at 6 months.

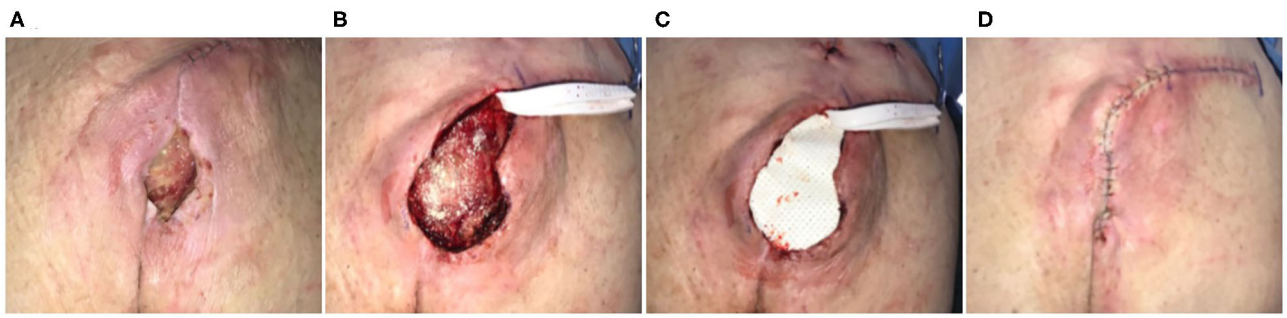


FIGURE 2 | Surgical reconstruction of recalcitrant sacral pressure injury. Case 2—**(A)** Eleven-month-old pressure injury that had previously failed a flap reconstruction 1 month prior; secondary procedure performed using ECM graft to stabilize the flap. **(B)** Excision of ulcer with partial ostectomy. **(C)** Placement of the ECM graft and **(D)** flap closure.

the coccyx, with a partial ostectomy (**Figure 2B**). An ECM graft (Myriad™, "Thick") was trimmed to fit the defect and into the base of the defect and covering the bone protrusion of the coccyx (**Figure 2C**). The excision was closed *via* a flap advancement with suture used to the close the primary incision line (**Figure 2D**). JP drains were placed and incisional NPWT initiated. A dehiscence of the site developed, which subsequently went onto heal *via* secondary intention at 3 months. At 6 months the defect remained healed.

Case 3

Twenty-six-year-old female with a 13-month-old non-healing full thickness defect following open reduction and internal fixation surgery of the left ankle (**Figure 3A**). Orthopedic hardware remained in place, and the wound was culture negative. The defect had previously been managed through use of alginate dressings. Surgical excision of proximal chronic tissues was carried out (**Figure 3B**). Trimmed ECM graft (Myriad™ "Thin") was placed contacting the tissues of the defect bed and allowed to rehydrate *in situ via* absorption of blood components (**Figure 3B**). The defect was closed by flap advancement (**Figure 3C**) and underwent incisional NPWT for seven days. The defect exhibited signs of infection and secondary dehiscence 1-week post-surgery (**Figure 3D**). Additional ECM graft material was packed in the dehiscence cavity (**Figure 3D**) and covered with a gentian violet/methylene blue foam secondary dressing. Over the following weeks, the defect demonstrated marked improvement with healthy granulation tissue development (**Figure 3E**). Therefore, application of additional ECM graft material, hydrolyzed collagen dressings covered with a non-adherent dressing layer and continued use of gentian violet/methylene blue secondary dressings were used to heal the defect *via* secondary intention. Successful closure of the defect by secondary intention was achieved 8 weeks after the initial flap surgery (**Figure 3F**).

DISCUSSION

We hypothesized that complications following flap reconstruction of chronic defects may be reduced by the complementary use of an ECM graft to stabilize and augment the surgical flap and underlying tissues. This pilot case series explored using a one-stage procedure of flap reconstruction augmented with ECM graft placement. Simultaneous use of ECM grafts in flap closure is scarcely documented in the literature. The use of an amnion-derived ECM graft material has been shown to improve random flap survival in a preclinical murine model (20), however, this work primarily focused on combination use

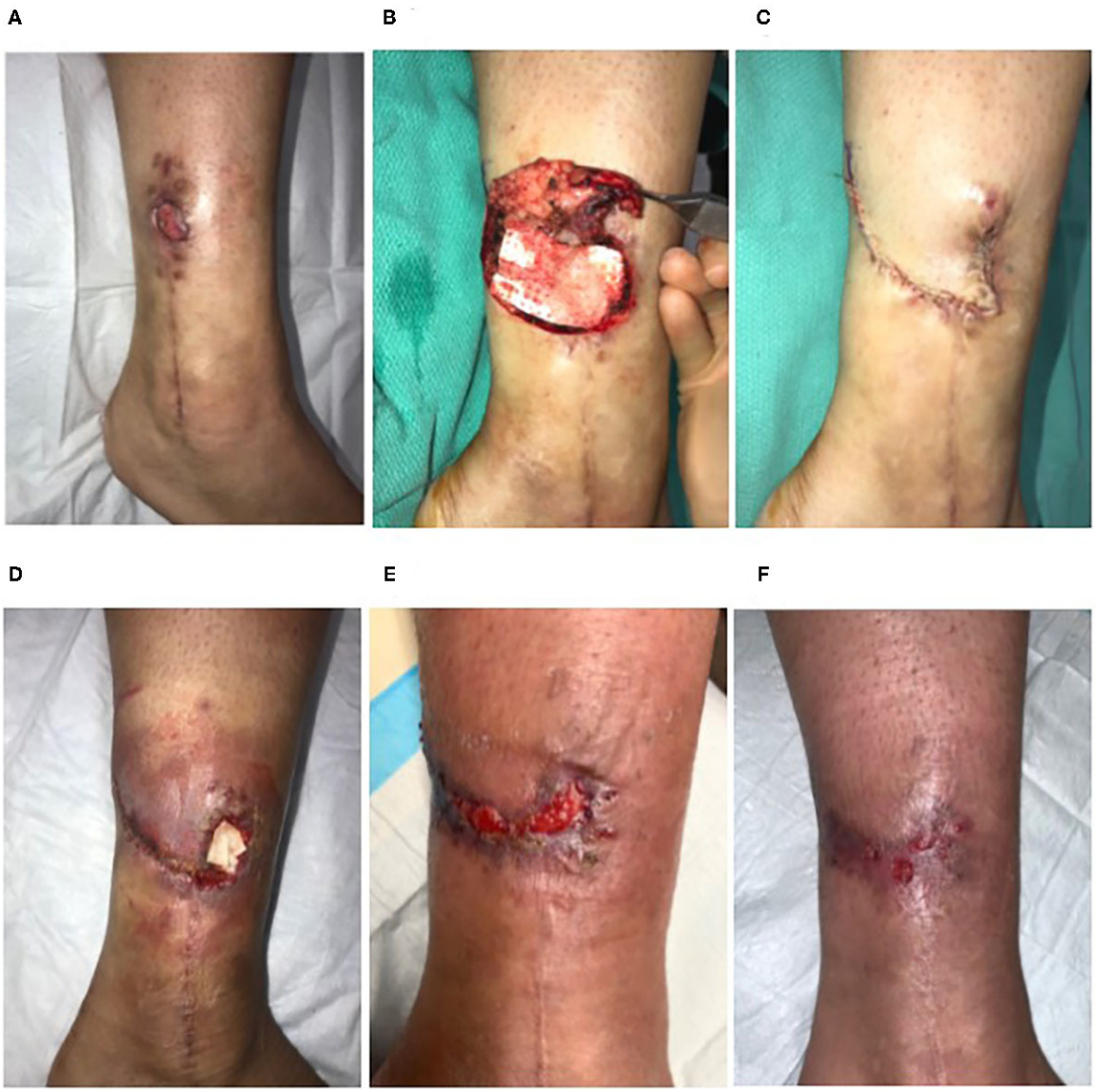


FIGURE 3 | Reconstruction of a non-healing lower extremity surgical defect. Case 3—**(A)** Thirteen-month-old non-healing defect following open reduction and internal fixation surgery of the left ankle. **(B)** Surgical excision of proximal chronic tissues and placement of the ECM graft into the defect. **(C)** Flap advancement and closure. **(D)** The defect exhibited signs of infection and secondary dehiscence 1-week post-surgery and was treated with a second ECM graft. **(E)** At 6 weeks, the defect demonstrated marked improvement with healthy granulation tissue development. **(F)** Successful closure of the defect by secondary intention was achieved 8-weeks after the initial flap reconstruction without additional surgical intervention.

of amnion graft with mesenchymal stem cell supplementation and has not been translated into human studies. Various clinical reports exist of utilizing ECM grafts in the salvage of compromised or failed flaps (21, 22), but these reports describe reactive use of an ECM graft in a second intervention rather than a deliberate initial strategy. In periodontal surgery, ECM grafts are commonly used in combination with coronally positioned flaps for the treatment of gingival recession, acting to provide root coverage and increase the thickness of the gingiva (23, 24).

To our knowledge this is the first published work regarding the use of ECM grafts to augment flap reconstruction. The ECM graft utilized in the current study is derived from ovine (sheep) forestomach tissue, specifically the propria submucosa, a layer of ECM that extends through the forestomach tissue (15). Once isolated the propria submucosa undergoes a decellularization process to remove the ovine cells and nucleic acids leaving a layer of intact ECM. Decellularization utilizes a combination of detergents, chelating agents and salts to firstly lyse the ovine cells, then solubilize the cell membranes and nucleic acids (15). Grafts

are fabricated using individual layers of ECM and presented either as a three- (∼1.0 mm) or five-layer graft (∼1.5 mm), in sizes up to 200 cm^2. While advanced ECM bioscaffolds have typically been difficult to access due to cost, pricing of the OFM ECM graft (∼USD$250–USD$2,500) enables novel usage of this technology in reconstructive procedures.

We hypothesized that an ECM graft may help to reduce flap complications *via* a combination of biological and physically mediated mechanisms. For example, the protease modulating effects of OFM (13) may rectify the underlying unbalanced environment in chronic soft tissue defects with high levels of tissue inflammation and proteolytic activity. Promotion of neovascularization by ECM material (16) may assist in establishment of blood supply from both the flap and the underlying tissues of the defect. Increasing the local blood supply to the defect through vascularization also minimizes risk of infection *via* increased perfusion of protective immune system elements and/or systemically administered antibiotics (25). Indeed, proper site preparation is vital for successful closure of chronic defects with positive post-debridement cultures being a proven predictor of failure of flap closure (26), as such our procedure included aggressive debridement and removal of chronic defective tissues. Additionally, placement of ECM graft material in the defect bed may provide occlusion of dead space between the flap and underlying soft tissues.

Results from the current pilot case series were encouraging, but the limited sample size must be noted. Additionally, five participants received incisional NPWT, the contribution of which cannot be fully assessed with this limited sample size. While incisional NPWT is known to reduce surgical site infections, the risk of dehiscence of surgical primary closures has been shown to be equivalent to standard wound dressings (27).

CONCLUDING REMARKS

Flap reconstruction is an effective and prevalent method for the repair of chronic soft tissue defects. The present case series piloted use of an ECM graft to augment flap reconstruction of chronic soft tissue defects. Outcomes of these initial cases may warrant future controlled studies for evaluation of this technique relative to unmodified flap closure.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

All patients provided written informed consent for their images and data to be used for research and publication purposes.

AUTHOR CONTRIBUTIONS

MD contributed to the design of the study, clinical management, data collection, data analysis, and preparation of the manuscript. KB and AW contributed to case management and data collection. KH, KD, and DG contributed to clinical management. All authors contributed to manuscript revision, read, and approved the submitted version.

FUNDING

MD received an educational travel grant from Aroa Biosurgery Limited.

ACKNOWLEDGMENTS

The authors acknowledge that assistance of Barnaby May and Christopher Miller (Aroa Biosurgery Limited) for assistance in the preparation of the manuscript.

REFERENCES

1. Tran BNN, Chen AD, Kamali P, Singhal D, Lee BT, Fukudome EY. National perioperative outcomes of flap coverage for pressure ulcers from 2005 to 2015 using American College of Surgeons National Surgical Quality Improvement Program. *Arch Plast Surg*. (2018) 45:418. doi: 10.5999/aps.2018.00262
2. Bamba R, Madden JJ, Hoffman AN, Kim JS, Thayer WP, Nanney LB, et al. Flap reconstruction for pressure ulcers: an outcomes analysis. *Plastic Reconstr Surg Glob Open*. (2017) 5:e1187. doi: 10.1097/GOX.0000000000001187
3. S. Badylak. The extracellular matrix as a scaffold for tissue reconstruction. *Semin Cell Dev Biol*. (2002) 13:377–460. doi: 10.1016/S1084952102000940
4. Ferreras DT, Craig S, Malcomb R. 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. *Surg Technol Int*. (2017) 30:61–9.
5. Bohn GA, Gass K. Leg ulcer treatment outcomes with new ovine collagen extracellular matrix dressing: a retrospective case series. *Adv Skin Wound Care*. (2014) 27:448–454. doi: 10.1097/01.ASW.0000453728.12032.6f
6. Liden BA, May BC. Clinical outcomes following the use of ovine forestomach matrix (endoform dermal template) to treat chronic wounds. *Adv Skin Wound Care*. (2013) 26:164–7. doi: 10.1097/01.ASW.0000428862.34294.d4
7. Simcock J, Than M, Ward B, May B. Treatment of ulcerated necrobiosis lipoidica with ovine forestomach matrix. *J Wound Care*. (2013) 22:383–4. doi: 10.12968/jowc.2013.22.7.383
8. González: Use of collagen extracellular matrix dressing for the treatment of a recurrent venous ulcer in a 52-year-old patient. *J Wound Ostomy Continence Nurs*. (2016) 43:310–2. doi: 10.1097/WON.0000000000000231
9. E. J. Lullove. 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. *Wounds*. (2017) 29:107–114.
10. Simcock J, May BC. Ovine forestomach matrix as a substrate for single-stage split-thickness graft reconstruction. *Eplasty*. (2013) 13:e58.
11. Ferzoco SJ. Early experience outcome of a reinforced bioscaffold in inguinal hernia repair: a case series. *Int J Surg Open*. (2018) 12:9–11. doi: 10.1016/j.ijso.2018.06.001
12. Sawyer MA. New ovine polymer-reinforced bioscaffold in hiatal hernia repair. *JSLS*. (2018) 22:e2018.00057. doi: 10.4293/JSLS.2018.00057

13. Negron L, Lun S, May BC. Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. *Int Wound J*. (2014) 11:392–7. doi: 10.1111/j.1742-481X.2012.01106.x
14. Street M, Thambyah A, Dray M, Amirapu S, Tuari D, Callon KE, et al. Augmentation with an ovine forestomach matrix scaffold improves histological outcomes of rotator cuff repair in a rat model. *J Orthop Surg Res*. (2015) 10:165. doi: 10.1186/s13018-015-0303-8
15. Lun S, Irvine SM, Johnson KD, Fisher NJ, Floden EW, Negron L, et al. A functional extracellular matrix biomaterial derived from ovine forestomach. *Biomaterials*. (2010) 31:4517–29. doi: 10.1016/j.biomaterials.2010.02.025
16. Irvine SM, Cayzer J, Todd EM, Lun S, Floden EW, Negron L, et al. Quantification of in vitro and in vivo angiogenesis stimulated by ovine forestomach matrix biomaterial. *Biomaterials*. (2011) 32:6351–61. doi: 10.1016/j.biomaterials.2011.05.040
17. Dempsey SG, Miller CH, Hill RC, Hansen KC, May BC. functional insights from the proteomic inventory of ovine forestomach matrix. *J Proteome Res*. (2019) 18:1657–68. doi: 10.1021/acs.jproteome.8b00908
18. Sizeland KH, Wells HC, Kelly SJ, Nesdale KE, May BC, Dempsey SG, et al. Collagen fibril response to strain in scaffolds from ovine forestomach for tissue engineering. *ACS Biomater Sci Eng*. (2017) 3:2550–8. doi: 10.1021/acsbiomaterials.7b00588
19. Floden EW, Malak SF, Basil-Jones MM, Negron L, Fisher JN, Lun S, et al. Biophysical characterization of ovine forestomach extracellular matrix biomaterials. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. (2011) 96:67–75. doi: 10.1002/jbm.b.31740
20. Chehelcheraghi F, Eimani H, Homayoonsadraie S, Torkaman G, Amini A, Majd HA, et al. Effects of acellular amniotic membrane matrix and bone marrow-derived mesenchymal stem cells in improving random skin flap survival in rats. *Iran Red Crescent Med J*. (2016) 18:e25588. doi: 10.5812/ircmj.25588
21. Shanti RM, Smart RJ, Meram A, Kim D. Porcine urinary bladder extracellular matrix for the salvage of fibula free flap skin paddle: technical note and description of a case. *Craniomaxillofac Trauma Reconstr*. (2017) 10:318–22. doi: 10.1055/s-0036-1593473
22. Kruper GJ, VandeGriend ZP, Lin H-S, Zuliani GF. Salvage of failed local and regional flaps with porcine urinary bladder extracellular matrix aided tissue regeneration. *Case Rep Otolaryngol*. (2013) 2013:917183. doi: 10.1155/2013/917183
23. Guan W, Liao H, Guo L, Wang C, Cao Z. Root coverage using a coronally advanced flap with or without acellular dermal matrix: a meta-analysis. *J Periodontal Implant Sci*. (2016) 46:22–34. doi: 10.5051/jpis.2016.46.1.22
24. de Queiroz Côrtes A, Sallum AW, Casati MZ, Nociti FH Jr, Sallum EA. A two-year prospective study of coronally positioned flap with or without acellular dermal matrix graft. *J Clin Periodontol*. (2006) 33:683–9. doi: 10.1111/j.1600-051X.2006.00969.x
25. Suh HP, Hong JP. The role of reconstructive microsurgery in treating lower-extremity chronic wounds. *Int Wound J*. (2019) 16:951–9. doi: 10.1111/iwj.13127
26. Shuck J, Nolan J, Kanuri A, Evans KK, Attinger CE. The effect of positive post-debridement cultures on local muscle flap reconstruction of the lower extremity. *Plastic Reconstr Surg*. (2015) 136:9–10. doi: 10.1097/01.prs.0000472283.01460.a1
27. Norman G, Goh EL, Dumville JC, Shi C, Liu Z, Chiverton L, et al. Negative pressure wound therapy for surgical wounds healing by primary closure. *Cochrane Database Syst Rev*. (2020) 6:CD009261. doi: 10.1002/14651858.CD009261.pub5

Conflict of Interest: MD consults for Aroa Biosurgery Limited (Auckland, New Zealand). Myriad^{TM} Soft Tissue Matrix was provided by Aroa Biosurgery Limited.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Surgical reconstruction of pilonidal sinus disease with concomitant extracellular matrix graft placement: a case series

Background: Pilonidal sinus disease (PSD) is a chronic inflammatory disease affecting the soft tissue of the sacrococcygeal region and remains a challenging disease for clinicians to treat. The optimal treatment for PSD remains controversial and recent reports describe several different surgical approaches offering different benefits. Approximately 40% of initial incision and drainage cases require subsequent surgery. Due to high recurrence rates and postoperative complications, a more complex revision surgery involving a flap reconstruction may be required. We hypothesised that the combination of an extracellular matrix (ECM) graft with tissue flap reconstruction may decrease the postoperative complications and recurrence rates for PSD.

Method: We report a retrospective case series using a surgical flap reconstruction with concomitant implantation of an ovine forestomach ECM graft under a fasciocutaneous flap with an off-midline closure for recurrent PSD, where previously surgical intervention had failed due to wound dehiscence and/or recurrent disease.

Results: The case series included six patients. After three weeks, all patients except one were fully healed, and the sixth was fully healed by week 4; all wounds remained fully healed at 12 weeks. All patients achieved good cosmesis and were able to return to normal function without any residual symptoms.

Conclusion: This pilot case series explored augmenting a flap reconstruction for complex PSD with advanced ECM graft materials, demonstrating that it may improve outcomes and minimise typical complications seen in flap closure, such as inflammation, infection, haematoma/seroma and hypoperfusion. Although the study had a limited number of participants, long-term outcomes were promising and suggest that further studies are warranted.

Declaration of interest: AEC has received educational travel grants from Aroa Biosurgery Limited. SGD and BAB are employees of Aroa Biosurgery Ltd. The authors have no other conflicts of interest.

ADM • acellular dermal matrix • CTP • dressing • extracellular matrix • flap • flap reconstruction • graft • infection • ovine forestomach matrix • pilonidal • pilonidal sinus • reconstructive surgery • skin substitute • wick-assisted closure • wound • wound healing

Pilonidal sinus disease (PSD) is a chronic inflammatory process involving the sacrococcygeal region that is characterised by highly inflamed soft tissue, recurrent infections and significantly reduced patient quality of life. The aetiology of PSD is relatively unknown. It is believed that PSD is an acquired condition relating to the presence of hair in the natal cleft which the body recognises as a foreign object, leading to the formation of midline pits with superseding secondary infection.[1] The infected follicle extends and ruptures into the subcutaneous tissue, forming a pilonidal abscess which can form a sinus track extending to deeper subcutaneous cavities. The challenge to clinicians who manage and treat these cases stems from the high risk of recurrence due to frequent pathogenic microbes and chronically inflamed tissue. Although PSD is a benign disorder, it can be very painful for patients, leading to absences from work or school, and may have a dramatic impact on quality of life. It is estimated that PSD has an incidence rate of 26 per 100,000[1] and affects roughly 70,000 patients annually in the US alone. Males are affected 4.1–8.1 times more frequently than females[2] and PSD commonly presents in the second decade of life. Risk factors include obesity, poor hygiene, familial history, repetitive irritation/trauma to the gluteal cleft and prolonged sitting.[3–5]

Treatment can be divided into two categories, operative and non-operative, but there tends to be some overlap between these two interventions. The non-operative management can range from a primary cyst curettage with adjunctive measures, such as laser hair epilation,[6] shaving the gluteal cleft[7] or phenol application.[8] Inevitably, when traditionally non-operative interventions fail, then surgical intervention is needed for the overwhelming majority of PSD cases. The mainstay of treatment for acute pilonidal disease or abscess is incision and drainage (I&D). After the acute inflammatory phase patients typically need to perform daily wound packing, dressing changes and take oral antibiotics for associated cellulitis.[9] Unfortunately,

Abigail E Chaffin,[1] MD, FACS, CWSP, FAPWCA; **Shane G Dowling**,[2] MSPAS, PA-C, CWS*; **Mychajlo S Kosyk**,[1] MD; **Brandon A Bosque**,[2] DPM, CWSP
***Corresponding author email:** shane.dowling@aroabio.com
1 Division of Plastic and Reconstructive Surgery, Tulane University School of Medicine, New Orleans, US. **2** Aroa Biosurgery Limited, Auckland, New Zealand.

simple I&D procedures are reported to have a 15–40% reoccurrence rate requiring revisional surgeries to remove residual debris, remnant sinus tracts and epithelialisation of the tissues.[10]

Surgical excision of chronic PSD is the current standard of care and the two techniques include surgical excision of diseased tissue with primary closure (including various flap techniques), versus excision with healing by secondary intention. There is a significant trend towards faster median healing times and decreased time for returning to work with the primary closure techniques.[11,12] Closure techniques have an impact on healing and recurrence rates. An off-midline closure seems to provide a clear benefit when compared to a midline closure, providing faster healing times, lower recurrence and lower rates of wound morbidity.[13] In complex chronic PSD where previous surgical treatment has failed, several flap-based treatment strategies have been described to provide healthy tissue coverage over the surgical defect. However, a potentially unfavourable outcome from this procedure is haematoma/seroma formation and wound dehiscence.[14]

A proposed solution to complications associated with flap reconstruction is the placement of an extracellular matrix (ECM) graft to augment the surgical flap and underlying tissues.[15,16] ECM grafts have been used in a variety of plastic and reconstructive surgery soft tissue repair given their innate ability to provide a scaffold for cellular infiltration and capillary formation.[17] There are many different ECM grafts clinically available that differ in their source (e.g., human, porcine, bovine, equine) and processing technique to decellularise the tissue to remove nuclear and cellular materials while preserving the structure and composition of the tissue ECM.

Ovine forestomach matrix (OFM) graft has shown promise in reducing complication rates when used during the surgical reconstruction of chronic soft tissues resulting from hidradenitis suppurativa (HS),[15] complex hard-to-heal wounds,[16] skin grafting[18] and abdominal wall repair.[19,20] OFM is a decellularised ECM graft that is a biomimetic of tissue ECM that has been shown to be anti-inflammatory through modulating protease activity,[21,22] stimulating angiogenesis, promoting cellular infiltration, and undergoing complete remodelling.[23]

The ability of the OFM graft to achieve these biological functions can be attributed to the 151 different matrisomal proteins that have been identified to date.[24] These include a wide variety of collagens, such as collagen I, III and IV, adhesion proteins and signalling molecules including, but not limited to, platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF2), epidermal growth factor (EGF) and

Table 1. Participant summary including demographic, surgical defect size and outcomes

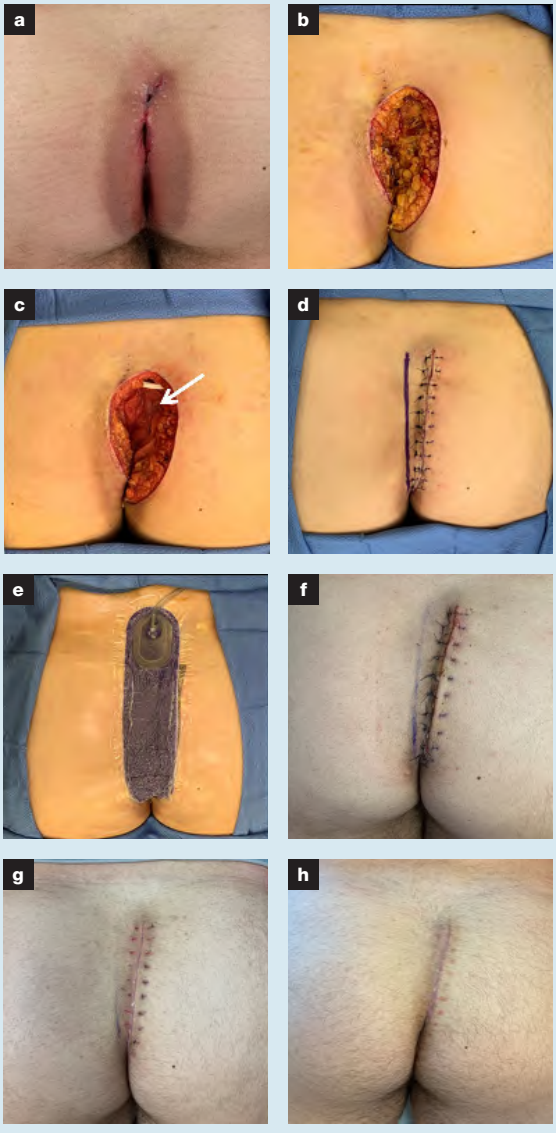
Gender/ age	Comorbidities	History	Area of diseased tissue	Outcomes
F, 21	Smoker Resumed smoking at <3 weeks post-operative	5 year history Prior I/D	~7×11cm	Minor dehiscence at 3 weeks Debrided and primarily reclosed No complication or recurrence at 40 weeks
M, 20 (Case 1)	None	2 year history Prior I/D Prior (12 month) excision and primary closure; dehisced	~12×6cm	Healed at 3 weeks No complication or recurrence at 40 weeks
M, 19	None	4 year history Prior I/D Prior (12 month) excision and primary closure; dehisced	~12×3cm	Healed at 3 weeks No complication or recurrence at 35 weeks
F, 52	Obesity Hidradenitis suppurativa	5 year history Prior I/D Prior (10 year) excision and primary closure; dehisced	~10×4cm	Minor complication at 1 week Closed without intervention Healed at 3 weeks No complication or recurrence at 12 weeks
M, 19 (Case 2)	Severe asthma Splenomegaly Gout	7 year history Prior I/D Prior (6 months) excision and primary closure; dehisced	~11×4cm	Healed at 3 weeks No complication or recurrence at 12 weeks
M, 15 (Case 3)	None	8 month history Prior I/D (2 months); NPWT resulting in severe pain at dressing change	~12×5cm	Healed at 3 weeks No complication or recurrence at 12 weeks

I/D—incision and drainage; F—female; M—male; NPWT—negative pressure wound therapy

connective tissue growth factor (CTGF).[18, 24] When used during the reconstruction of chronic soft tissues, the aim of the OFM graft is to reduce surgical complications by suppressing tissue inflammation, filling surgical dead space and rapidly forming well-vascularised new tissue within the defect.

In this retrospective case series, we present a novel use of an OFM graft to aid in the soft tissue flap reconstruction of complex chronic PSD. We employed a wide excision of the chronically inflamed tissue, OFM graft placement at the base of the defect, perforator artery-sparing gluteal fasciocutaneous flap advancement, wick-assisted off-midline closure and incisional negative pressure wound therapy (NPWT).

Fig 1. Representative images of Case 1. Initial defect (**a**); post wide excision, defect measuring 12×6×5cm (**b**); placement of the ovine forestomach matrix (OFM) graft at the base of the defect (arrow) (**c**); fasciocutaneous flap advancement and closure (**d**); incisional negative pressure wound therapy (NPWT) device (**e**); postoperative at week 1 (**f**); fully healed at postoperative week 3 (**g**); postoperative at week 10 (**h**)



Methods

Ethical approval

All patients provided written informed consent for their photographs and data to be used for research and publication purposes. The study was conducted in accordance with World Medical Association Declaration of Helsinki ethical guidelines.

Data collection

Retrospective data were collected from operative notes, clinical follow-up notes and clinical photography. All patients were taken to the operating room and the surgical site was prepared with chlorhexidine gluconate (CHG), and all patients received a single dose of appropriate prophylactic antibiotics. Through an off-midline approach, all the chronically inflamed tissue was removed via a wide excision down to the sacral fascia. A combination of manual palpation of indurated tissue and the injection of methylene blue into sinus tissues was used to help delineate the area of resection. A 10cm×10cm OFM ECM graft (Myriad Soft Tissue Matrix, Aroa Biosurgery Limited, New Zealand) was rehydrated in sterile saline (~5 minutes), trimmed to size, then placed into the base of the defect. The graft was anchored to the deep sacral fascia and medial gluteal fascia using interrupted 2-0 Vicryl (Ethicon, US) sutures. A gluteal fasciocutaneous advancement flap was raised, sparing the inferior and/or superior gluteal artery perforating blood vessels, and advanced over the graft. Deep quilting 0 PDS II (Ethicon, US) sutures were secured in a progressive tension fashion to immobilise and advance the flap. A size 15FR Blake drain was placed with a tunnelled exit point in the lateral aspect of the wound and secured using nylon suture (3-0) and connected to a bulb suction device. The dermal layer was closed using interrupted 3-0 Monocryl suture (Ethicon, US) and the skin was closed using 2-0 nylon suture, using a vertical mattress technique. Two patients had half-inch Iodoform (Integrity Medical Devices Inc., US) wicks placed at a depth of ~1cm, between the vertical mattress sutures (e.g. Fig 3d). All patients received closed incision NPWT (Prevena, 3M+KCI, US) which remained in place for one week.

Patients were followed up at a one-week postoperative visit for NPWT and drain removal and then were followed for at least 12 weeks to monitor for dehiscence, infection or recurrence.

Results

A total of six patients were included in this case series (Table 1). The median age of patients was 25 years old. All patients had previously undergone I&D procedures and four patients had previously undergone a primary closure that had failed/dehisced at an outside institution. There was a variety of chronicity to the

Fig 2. Representative images of Case 2. Initial defect (**a**); indicating the off-midline excision (**b**); post wide excision, defect measuring 11×5×6cm (**c**); placement of the ovine forestomach matrix (OFM) graft at the base of the defect (arrow) (**d**); fasciocutaneous flap advancement and off-midline closure (**e**); incisional negative pressure wound therapy (NPWT) device (**f**); postoperative at week 1 (**g**); fully healed at postoperative week 4 (**h**)

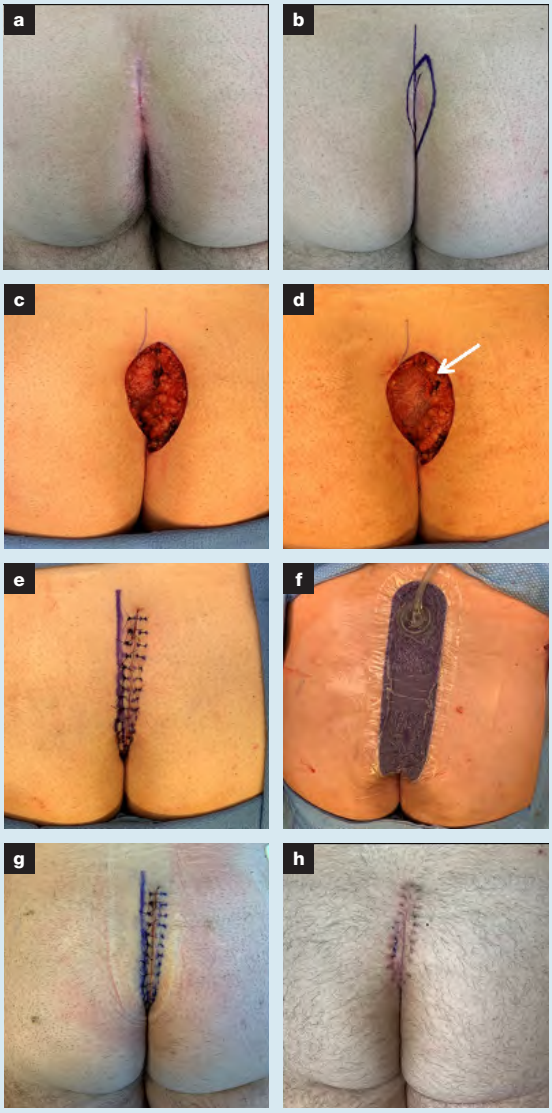
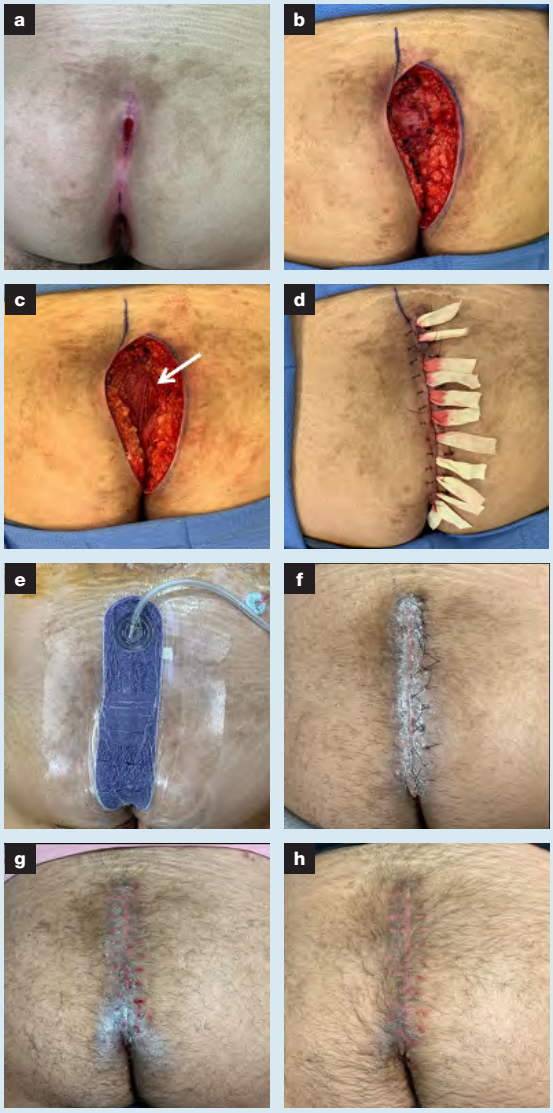


Fig 3. Representative images of Case 3. Initial defect (**a**); post wide excision, defect measuring 15×6×5cm (**b**); placement of the ovine forestomach matrix (OFM) graft at the base of the defect (arrow) (**c**); fasciocutaneous flap advancement and wick-assisted off-midline closure (**d**); incisional negative pressure wound therapy (NPWT) device (**e**); postoperative at week 2 (**f**); fully healed at postoperative week 5 (**g**); postoperative at week 8 (**h**)



wounds, with the longest being seven years old. Post wide excision, defects ranged in size from 36–77cm^2. Using this flap strategy, a fully healed incision was achieved for all but one patient by the three-week point. The one minor dehiscence at week 3 was resolved without further surgical intervention. All wounds remained fully healed at week 12. All surgical wounds demonstrated good cosmesis compared to adjacent tissue. The healed incisions demonstrated excellent functionality and all patients were satisfied with their respective outcomes.

Case 1

A 20-year-old male athlete with no significant comorbidities who had a 2-year history of PSD and had undergone multiple prior I&D procedures with the most recent being 12 months prior to presentation. At that time, a primary midline closure was attempted that dehisced early in the postoperative period and was being managed by NPWT. The chronic sinus was draining purulent material prior to surgery (Fig 1a). The patient had significant discomfort with any sitting and was not able to compete in athletics due to the wound.

Wide excision gave a defect measuring 12×6×5cm (Fig 1b). The deep wound was irrigated with a dilute chlorhexidine solution (Irrisept, Innovation Technologies, Inc., US) followed by a 50/50 povidone-iodine (Betadine, Alcon Laboratories Inc., US) and saline solution soak. The OFM graft was rehydrated, trimmed and secured in the defect (Fig 1c) as described above, followed by advancement of a fasciocutaneous flap (12×10cm) elevated from the right buttock, sparing the superior gluteal artery perforator, and an off-midline closure (Fig 1d). The wound was then dressed with a silver dressing (Mepitel Ag, Mölnlycke Health Care AB, US) and an incisional NPWT was placed (Fig 1e). The patient was followed up one-week post-operation for NPWT and drain removal. There was minimal erythema, no dehiscence and the patient reported no pain (Fig 1f). Sutures were removed at week 3 (Fig 1g) and the wound remained healed at week 10 (Fig 1h). At 40-week long-term follow-up there were no complications or recurrence.

Case 2

A 19-year-old male with a past medical history significant for severe asthma, currently on dupilumab (Dupixent, Sanofi, France), with a history of gout, splenomegaly, and PSD for 7 years. The patient had undergone multiple rounds of oral antibiotics and had undergone surgical excision of the cyst followed by a midline closure six months prior to presentation. When sutures were removed at week 2 post-operation, the wound had dehisced within the first 24 hours, and since this time the wound was being managed with wet to dry dressings and oral antibiotics. The wound continued to drain, and a culture was positive for methicillin-resistant *Staphylococcus aureus* (MRSA) (Fig 2a). The patient had severe pain and elected to proceed with a re-excision of the PSD and flap reconstruction with an off-midline closure (Fig 2b). A wide excision of the cysts extending down the sacral fascia was completed and the resulting wound measured 11×5×6cm (Fig 2c). The OFM graft was rehydrated, trimmed, and secured in the defect (Fig 2d) as described above, followed by advancement of a fasciocutaneous flap (12×10cm) elevated from the left buttock, sparing the inferior gluteal artery perforator, and an off-midline closure (Fig 2e), and dressed with a non-adherent and incisional NPWT (Fig 2f). The patient was followed up one week post-operation for NPWT and drain removal with minimal erythema, no wound dehiscence and reported no pain. At week 4 post-operation, sutures were removed (Fig 2h) and the wound remained healed at week 12 without any reoccurrence.

Case 3

A 19-year-old male with no significant past medical history presenting with an 8-month history of a draining PSD abscess after an I&D (Fig 3a). Due to the persistent drainage the patient underwent an attempted cyst excision two months prior to presentation with a plan to heal the wound by secondary intention through NPWT. The patient admitted to severe pain requiring anaesthesia at NPWT dressing changes. Due to these factors the patient elected to proceed with a wide excision and closure. During the wide excision of the cyst, another sinus tract was found that tunnelled an additional 4.5cm cephalad to the anal verge leading to a 15×6×5cm defect (Fig 3b). The OFM graft was rehydrated, trimmed and secured in the defect (Fig 3c) as described above, followed by advancement of a fasciocutaneous flap (12×10cm) elevated from the left buttock, sparing the inferior gluteal artery perforator, and an off-midline closure with the addition of Iodoform wicks (Fig 3d). The wound was dressed with an incisional NPWT and the patient was placed on Bactrim DS (Sun Pharmaceutical Industries Inc. India) twice daily for seven days. One-week post-operation, there was mild erythema present. Sutures were removed at week 3 and the patient was placing zinc ointment on the incision daily. The incision remained closed at a 12-week follow-up visit.

Discussion

PSD mainly affects the young male patient population with a rate of 4.1 to 8.1 times greater for males than females.[2] There is no current consensus on the incidence of PSD, with reported incidences ranging from 26 per 100,000[1] to as high as 700 per 100,000.[25]

PSD presents a challenge to clinicians due to its high rates of recurrence and surgical wound complications.[10] These complications have been attributed to risk factors such as obesity, smoking, family history, poor hygiene, sinus size and previous surgical excisions.[3–5,25] Although I&D of a pilonidal abscess helps alleviate pain and avoid a septic infection, it does not address the underlying problem and can lead to a chronically inflamed soft tissue envelope.[26] For these reasons, a more complex soft tissue reconstructive approach has been suggested to mitigate these problems and is an attempt to remove all the diseased tissue to prevent reoccurrence.

There are a multitude of surgical techniques that are suggested to reduce postoperative complication rates following surgical reconstruction of PSD.[1] In this case series, we investigated the benefit of a modified flap technique previously described for hidradenitis suppurativa (HS) and complex hard-to-heal wound reconstruction.[15,16] We have chosen this technique due to the chronic inflammatory response and bacterial contamination seen in HS and PSD. Both disease processes lead to the creation of 'pits' in the subcutaneous space which, when contaminated by bacteria, become painful abscesses that are challenging to manage with standard wound care. OFM has shown promise in reducing postoperative complications in HS and complex hard-to-heal wounds through its ability to modulate the inflammatory response in these chronically inflamed soft tissues, fill surgical dead space and rapidly regenerate soft tissues.[15,16,21]

OFM is known to contain a number of naturally

occurring anti-inflammatory proteins[24] and has been shown to balance soft tissue proteases through broad spectrum modulation of matrix metalloproteinases and neutrophil elastase.[21] The biology and structure of OFM, including residual vascular channels, may establish increased perfusion within the fasciocutaneous flap at an earlier time point.[23] Additionally, the placement of the ECM graft material may lead to a decrease in the dead space that can occur after a wide excision, therefore decreasing the risk of seroma/haematoma formation.[16]

The recurrence rates for PSD after lay open and primary closure techniques are 17% and 30%, respectively.[27] There are two different techniques to achieve closure for PSD, a lateralised off-midline closure with flattening of the natal cleft and a midline incision that falls in line with the native cleft. When comparing the reoccurrence rates of these two approaches, the latter has a significantly higher rate of 7–40% compared to 0–3% seen with the off-midline approach.[27]

A large meta-analysis of RCT and non RCT studies, which included 89,583 patients who underwent either a Karydakis or Bascom flap procedure, had a reoccurrence rate of 0.2% at 12 months, 0.6% at 24 months and 2.7% at 120 months.[29] In the same paper, Stauffer et al.[28] evaluated the recurrence rate for a primary midline closure to be 3.4% at 12 months, 7% at 24 months, 32% at 120 months and more than doubling to 67.9% at 240 months.[28] In our case series presented here we had a 0% recurrence rate at 12 weeks postoperatively.

The two patients whose incisions were closed using wick-assisted closure both achieved complete closure and remained closed at the 12-week mark. The purpose of the wick, to remove excess fluid accumulation and optimise the wound healing environment, has been demonstrated in a similar chronically inflamed tissue pathology, HS, with successful wide excision and subsequent wick-assisted closure technique.[15]

Study limitations

Although results from this pilot case series are promising, a long-term follow-up is needed to assess the overall reoccurrence rate compared to the current literature. Ideally, follow-up would occur at 12, 24 and 60 months. One other limitation is the small sample size in our case series. The concurrent use of closed incisional NPWT was employed on all patients, upon which we cannot draw a conclusion given the limited sample size. Some of the desired benefits of NPWT were to have a sterile dressing to cover the incision for seven days, therefore providing a barrier to any faecal contamination in the early postoperative period while also being able to improve the blood flow to the incision site. While NPWT has been shown to decrease surgical site infections, there has been no benefit in preventing wound dehiscence when compared to standard wound dressing.[29]

Conclusions

Flap reconstruction of PSD and recurrent PSD has demonstrated the ability to lower the its recurrence rate. This present case series demonstrates the first known use of an ECM graft to augment flap reconstruction in PSD. Our initial findings using the OFM graft as part of our surgical flap reconstruction of these affected patients is very encouraging. A larger case study with long-term follow-up of patients treated with OFM graft would be a valuable tool to access improvements in the rate of recurrence of the disease and complications after surgical intervention with OFM. JWC

Acknowledgements: The authors would like to acknowledge Aroa Biosurgery Limited (New Zealand) for assistance in the preparation of this manuscript.

References

1 Bi S, Sun K, Chen S, Gu J. Surgical procedures in the pilonidal sinus disease: a systematic review and network meta-analysis. Sci Rep 2020; 10(1):13720. https://doi.org/10.1038/s41598-020-70641-7
2 Osmanoglu G, Yetisir F. Limberg flap is better for the surgical treatment of pilonidal sinus. Results of a 767 patients series with an at least five years follow-up period. Chirurgia (Bucur) 2011; 106(4):491–494
3 Yildiz T, Elmas B, Yucak A et al. Risk factors for pilonidal sinus disease in teenagers. Indian J Pediatr 2017; 84(2):134–138. https://doi.org/10.1007/s12098-016-2180-5
4 Søndenaa K, Andersen E, Nesvik I, Søreide JA. Patient characteristics and symptoms in chronic pilonidal sinus disease. Int J Colorectal Dis 1995; 10(1):39–42. https://doi.org/10.1007/BF00337585
5 Hyppolito da Silva J. Pilonidal cyst: cause and treatment. Dis Colon Rectum 2000; 43(8):1146–1156. https://doi.org/10.1007/BF02236564
6 Badawy EA, Kanawati MN. Effect of hair removal by Nd:YAG laser on the recurrence of pilonidal sinus. J Eur Acad Dermatol Venereol 2009; 23(8):883–886. https://doi.org/10.1111/j.1468-3083.2009.03147.x
7 Hull TL, Wu J. Pilonidal disease. Surg Clin North Am 2002; 82(6):1169–1185. https://doi.org/10.1016/S0039-6109(02)00062-2
8 Dogru O, Camci C, Aygen E et al. Pilonidal sinus treated with crystallized phenol: an eight-year experience. Dis Colon Rectum 2004; 47(11):1934–1938. https://doi.org/10.1007/s10350-004-0720-y
9 Khanna A, Rombeau J. Pilonidal disease. Clin Colon Rectal Surg 2011; 24(1):046–053. https://doi.org/10.1055/s-0031-1272823
10 Fitzpatrick EB, Chesley PM, Oguntoye MO et al. Pilonidal disease in a military population: how far have we really come? Am J Surg 2014; 207(6):907–914. https://doi.org/10.1016/j.amjsurg.2013.07.038
11 Rao MM, Zawislak W, Kennedy R, Gilliland R. A prospective randomised study comparing two treatment modalities for chronic pilonidal sinus with a 5-year follow-up. Int J Colorectal Dis 2010; 25(3):395–400. https://doi.org/10.1007/s00384-009-0804-1
12 Hosseini SV, Bananzadeh AM, Rivaz M et al. The comparison between drainage, delayed excision and primary closure with excision and secondary healing in management of pilonidal abscess. Int J Surg 2006; 4(4):228–231. https://doi.org/10.1016/j.ijsu.2005.12.005
13 Abu Galala KH, Salam IM, Abu Samaan KR et al. Treatment of pilonidal sinus by primary closure with a transposed rhomboid flap compared with deep suturing: a prospective randomised clinical trial. Eur J Surg 1999; 165(5):468–472. https://doi.org/10.1080/110241599750006721
14 Käser SA, Zengaffinen R, Uhlmann M et al. Primary wound closure with a Limberg flap vs. secondary wound healing after excision of a pilonidal sinus: a multicentre randomised controlled study. Int J Colorectal Dis 2015; 30(1):97–103. https://doi.org/10.1007/s00384-014-2057-x
15 Chaffin AE, Buckley MC. Extracellular matrix graft for the surgical management of Hurley stage III hidradenitis suppurativa: a pilot case series. J Wound Care 2020; 29(11):624–630. https://doi.org/10.12968/jowc.2020.29.11.624
16 Desvigne MN, Bauer K, Holifield K et al. Case report: Surgical closure

Reflective questions

- Pilonidal sinus disease (PSD) has a significant impact on patients' quality of life, especially at a young age, and often PSD patients require frequent surgical procedures to cure the disease. Should surgical flap reconstruction be considered earlier in the treatment course for recurrent PSD?
- Does the addition of a wick-assisted closure lead to a higher rate of wound closure in the acute postoperative phase?
- Surgical reconstruction involving inflamed tissue like that seen in PSD often suffers from increased complication rates (e.g., infection, dehiscence or seroma). Should the inclusion of advanced extracellular matrix (ECM) technology to counteract tissue inflammation be considered more often for these types of surgeries?

of chronic soft tissue defects using extracellular matrix graft augmented tissue flaps. Front Surg 2021; 7(173):559450. https://doi.org/10.3389/fsurg.2020.559450
17 Badylak SF. The extracellular matrix as a scaffold for tissue reconstruction. Semin Cell Dev Biol 2002; 13(5):377–383. https://doi.org/10.1016/S1084952102000940
18 Lun S, Irvine SM, Johnson KD et al. A functional extracellular matrix biomaterial derived from ovine forestomach. Biomaterials 2010; 31(16):4517–4529. https://doi.org/10.1016/j.biomaterials.2010.02.025
19 Ferzoco SJ. Early experience outcome of a reinforced bioscaffold in inguinal hernia repair: a case series. Int J Surg Open 2018; 12:9–11. https://doi.org/10.1016/j.ijso.2018.06.001
20 Sawyer MA. New ovine polymer-reinforced bioscaffold in hiatal hernia repair. JSLS 2018; 22(4):e2018.00057. https://doi.org/10.4293/JSLS.2018.00057
21 Negron L, Lun S, May BCH. Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. Int Wound J 2012; 11(4):392–397. https://doi.org/10.1111/j.1742-481X.2012.01106.x
22 Street M, Thambyah A, Dray M et al. Augmentation with an ovine forestomach matrix scaffold improves histological outcomes of rotator cuff repair in a rat model. J Orthop Surg Res 2015; 10(1):165. https://doi.org/10.1186/s13018-015-0303-8
23 Irvine SM, Cayzer J, Todd EM et al. Quantification of in vitro and in vivo angiogenesis stimulated by ovine forestomach matrix biomaterial. Biomaterials 2011; 32(27):6351–6361. https://doi.org/10.1016/j.biomaterials.2011.05.040
24 Dempsey SG, Miller CH, Hill RC et al. Functional insights from the proteomic inventory of ovine forestomach matrix. J Proteome Res 2019; 18(4):1657–1668. https://doi.org/10.1021/acs.jproteome.8b00908
25 Onder A, Girgin S, Kapan M et al. Pilonidal sinus disease: risk factors for postoperative complications and recurrence. Int Surg 2012; 97(3):224–229. https://doi.org/10.9738/CC86.1
26 Jensen SL, Harling H. Prognosis after simple incision and drainage for a first-episode acute pilonidal abscess. Br J Surg 2005; 75(1):60–61. https://doi.org/10.1002/bjs.1800750122
27 Uçar AD, Carti EB, Oymaci E et al. Recurrent pilonidal disease surgery: is it second primary or reoperative surgery? Turkish J Surg 2016; 32(3):162–167. https://doi.org/10.5152/UCD.2015.3112
28 Stauffer VK, Luedi MM, Kauf P et al. Common surgical procedures in pilonidal sinus disease: a meta-analysis, merged data analysis, and comprehensive study on recurrence. Sci Rep 2018; 8(1):3058. https://doi.org/10.1038/s41598-018-20143-4
29 Norman G, Goh EL, Dumville JC et al. Negative pressure wound therapy for surgical wounds healing by primary closure. Cochrane Database Syst Rev 2020; 6:CD009261. https://doi.org/10.1002/14651858.CD009261.pub6

Surgical Management of Hidradenitis Suppurativa: A Two-Center Retrospective Study

Ryoko Hamaguchi, M.D.
Taylor L. Wearda, M.D.
Angela S. Volk, M.D.
Kimberly M. Kramer, M.P.H.
Alexa B. Kimball, M.D., M.P.H.
Abigail E. Chaffin, M.D.
Dennis P. Orgill, M.D., Ph.D.

Boston, Mass.; and New Orleans, La.

Background: Hidradenitis suppurativa is a chronic inflammatory condition that presents a challenging reconstructive problem for plastic surgeons.
Methods: The authors performed a retrospective chart review of hidradenitis suppurativa patients managed with surgical excision between 2005 and 2020 at Brigham and Women's Hospital and Tulane University Medical Center. Operative cases associated with the same hospitalization were organized into treatment episodes and assessed for patient demographics, operative techniques, and outcomes.
Results: A total of 181 patients, 435 cases and 316 treatment episodes (Brigham and Women's Hospital, n = 269; Tulane University Medical Center, n = 47), were identified across two diverse institutions. Their respective series showed comparable patient demographics, and 94 percent of the combined episodes achieved wound closure and healing during the study period. Several techniques of closure were identified, including immediate closure and site-specific methods, such as an expedited staged closure using internal negative-pressure wound therapy as a temporary bridge, "recycled" skin grafting, and repurposing iodoform wicks as an adjunct wound healing therapy to immediate closure.
Conclusions: This large multi-institutional retrospective chart review on the plastic surgical management of hidradenitis suppurativa demonstrates that surgery is an effective therapy for hidradenitis suppurativa and captures a diversity of site-specific techniques that may serve as a foundation for future prospective studies and evidence-based guidelines for the use of various techniques to optimize patients' surgical outcomes. (*Plast. Reconstr. Surg.* 150: 1115, 2022.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Hidradenitis suppurativa is a debilitating chronic inflammatory condition of the follicular pilosebaceous units, characterized by nodules, scars, abscesses, and sinus tracts in areas such as the axillae, groin, perineum, and gluteal and pannicular areas.[1] Studies have demonstrated the condition's devastating impact on the patient's quality of life, sometimes leading to clinical depression. Hidradenitis suppurativa is associated with lifestyle factors such as smoking and medical comorbidities such as obesity, diabetes, polycystic ovarian syndrome, and inflammatory bowel disease.[2]

The Hurley staging system describes hidradenitis suppurativa disease severity, ranging from mild disease with nodules and abscesses (stage I) to severe disease with widespread scars and sinus tract formation (stage III).[3] Despite the availability of pharmacologic agents for hidradenitis suppurativa—including antibiotics, steroids, and

From Harvard Medical School; the Division of Plastic and Reconstructive Surgery, Tulane University School of Medicine; Division of Plastic Surgery, Brigham and Women's Hospital; and Department of Dermatology, Beth Israel Deaconess Medical Center.
Received for publication October 20, 2020; accepted December 22, 2021.

DOI: 10.1097/PRS.0000000000009658

Disclosure: *Dr. Kimball is a consultant and investigator for AbbVie, Bristol Myers Squibb, Janssen, Eli Lilly, Novartis, Pfizer, and UCB; investigator for Incyte and Anapyts Bio; consultant for Alumis, Bayer, Boehringer Ingelheim, Ventyx, Moonlake, Concert, Sonoma Bio, and Sanofi; receives fellowship funding from Janssen; and serves on the Board of Directors for Almirall. Dr. Chaffin is a consultant for Aroa Biosurgery. Dr. Orgill receives research funding from Acelity, Inc., through grants to Brigham and Women's Hospital. The remaining authors have no financial disclosures relevant to the content of this article.*

Related digital media are available in the full-text version of the article on www.PRSJournal.com.

biologics such as adalimumab—the cessation of therapies often leads to recurrence.[4] Wide local excision remains the standard for chronic hidradenitis suppurativa,[5] and reconstruction can be performed through primary closure, delayed or staged closure, local flaps,[6,7] perforator flaps,[8,9] and skin grafts. Although immediate primary closure is preferred (as it eliminates the need for painful dressing changes), larger or infected wounds may require delayed or staged procedures, sometimes using negative-pressure wound therapy as a bridge to definitive closure. In a retrospective study of 27 hidradenitis suppurativa patients, those managed with delayed primary closure using negative-pressure wound therapy had healing times comparable to those treated with immediate primary closure, with no disease recurrence. In this study, authors recommend treating postexcision wounds with negative-pressure wound therapy for 2 to 4 days before definitive closure for wounds larger than 70 cm^2 or with persistent infection.[10] Others have reused the skin of excised diseased tissue as a skin graft, removing the diseased folliculopilosebaceous units before inset. In addition to case reports of recycled skin grafting in perianal and gluteal hidradenitis suppurativa,[11,12] a retrospective study demonstrated the successful use of recycled full-thickness skin grafts in 18 patients with gluteal hidradenitis suppurativa, with no recurrence over a 61.3-month follow-up period.[13] This may provide an avenue for coverage while eliminating donor-site morbidity in severe cases with minimal healthy donor tissue.

Although several retrospective studies on the surgical management of hidradenitis suppurativa exist, many of these are relatively small (<100 patients),[10,14,15] and many larger studies fail to quantify detailed postoperative outcomes such as time to healing.[16–19] Furthermore, although studies have examined the outcomes of healing by secondary intention with serial dressing changes, there are few large studies examining patients undergoing negative-pressure wound therapy as a bridge to definitive closure.[20] In this study, we attempt to fill this gap and add to the existing body of literature by describing the operative approaches and outcomes of patients undergoing surgical management of hidradenitis suppurativa in two large academic medical centers.

PATIENTS AND METHODS

We performed an institutional review board–approved retrospective chart review of all hidradenitis suppurativa cases managed with surgical excision between July of 2005 and February of 2020. Patients undergoing wide local excision, breast reduction, or panniculectomy with hidradenitis suppurativa as the primary indication were included, whereas those undergoing incision and drainage or surgical unroofing were excluded. We examined cases performed by the senior authors (D.P.O. and A.E.C.) and a former senior partner (R.E.N.) at the Brigham and Women's Hospital and Tulane University School of Medicine, respectively.

A "treatment episode" was defined as a patient encounter encompassing all interventions performed for a planned treatment during a single hospitalization. For instance, a wide local excision with temporary negative-pressure wound therapy and a subsequent return to the operating room during the same hospitalization for definitive closure was considered one episode. For each episode, we collected information regarding total surface area excised, anatomical site involvement, closure type, and reconstructive modalities used, including negative-pressure wound therapy, skin grafts, and/or flap closure. Excisional sites included the axilla, perineum, groin/thighs, penoscrotal area, buttocks, abdomen, breast, and the head/neck/scalp, where surgical involvement of the bilateral axillae and/or breasts was quantified as two separate anatomical sites. For each treatment episode, adequate follow-up was defined as a minimum of 2 months by the primary surgeon or by a collaborating dermatology provider, with the exception of patients who achieved healing or required reoperation before this 2-month time point, who were included in the study (Fig. 1). Healing was defined as documentation of complete wound closure or 1 cm^2 or less of open area with no other complications at final follow-up. Postoperative complications were defined as failed healing at final follow-up or any of the following during the postoperative 30-day period: delayed healing (wound dehiscence or other persistent open areas), bleeding, infection, seroma or hematoma, hypertrophic granulation tissue, or new local disease. These criteria were applied uniformly to both cohorts, to minimize misclassification bias arising from data collected from varying electronic health record systems.

Statistical analysis was performing using the two-tailed, unpaired *t* test, chi-square test, or Fisher's exact test of independence with GraphPad Prism version 9.00 for MacOS (GraphPad Software, Inc., La Jolla, Calif.). For the interinstitutional follow-up and healing time comparison,

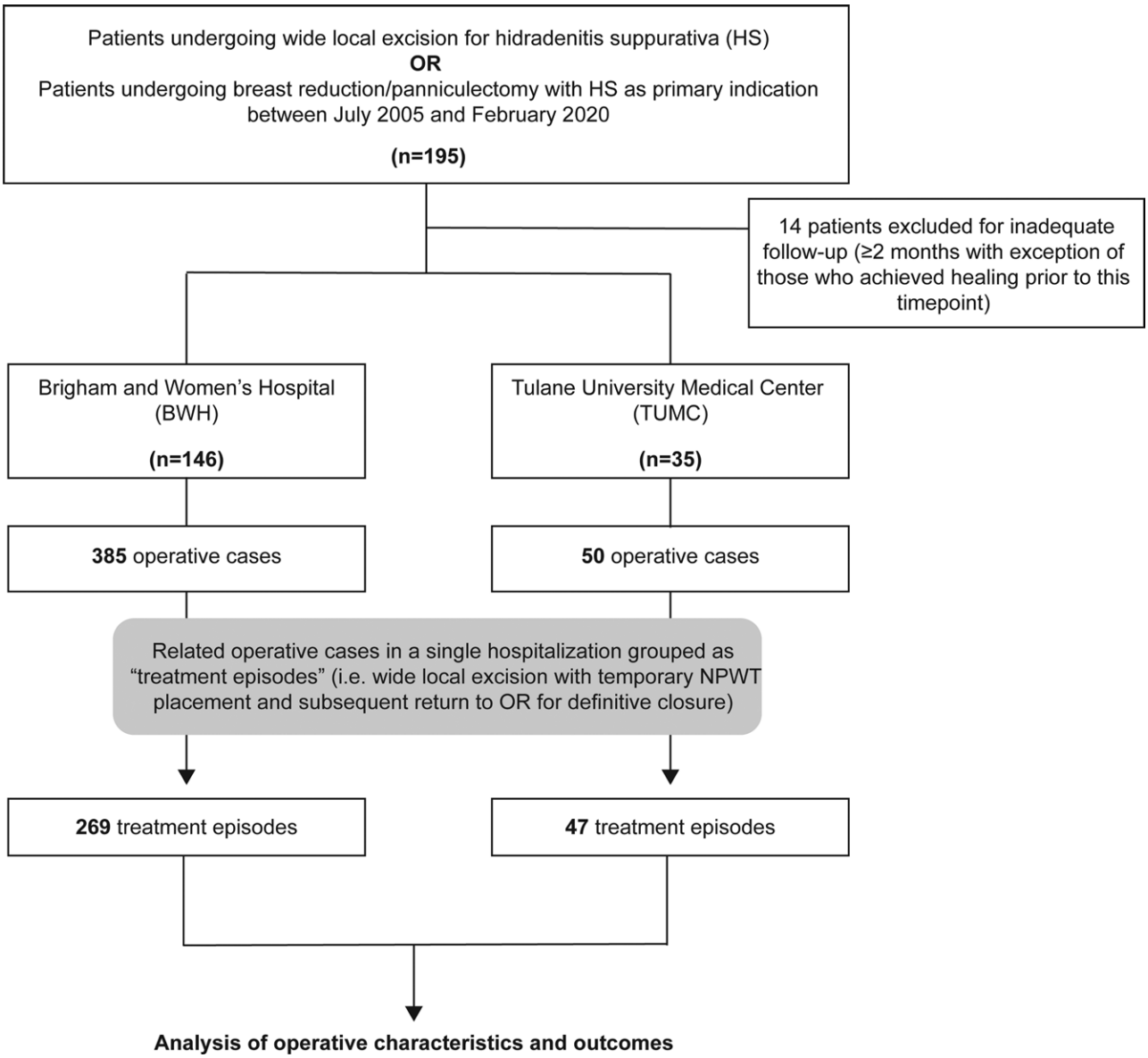


Fig. 1. Study design. A total of 181 patients were identified across two geographically disparate academic centers, excluding patients who did not fulfill follow-up criteria. The number of individual operative cases surpassed the number of patients, and related cases occurring during the same hospitalization were organized into treatment episodes. Treatment episodes were evaluated for parameters such as total excisional area, healing status, and time.

a D'Agostino-Pearson test was used to assess for normality and the Mann-Whitney test was used in lieu of an unpaired t test. A significance level of $p = 0.05$ was used for all analyses.

RESULTS

Patient Demographics and Clinical Characteristics

Four hundred seven operative cases in 155 patients and 57 cases in 40 patients at Brigham and Women's Hospital and Tulane University Medical Center, respectively, were identified. Ninety-four percent of the Brigham and Women's Hospital and 88 percent of the Tulane University Medical Center patients achieved adequate follow-up, yielding a final total of 181 patients (Brigham and Women's Hospital, $n = 146$; Tulane University Medical Center, $n = 35$), 435 cases (Brigham and Women's Hospital, $n = 385$; Tulane University Medical Center, $n = 50$), and 316 treatment episodes (Brigham and Women's Hospital, $n = 269$; Tulane University Medical Center, $n = 47$), with median follow-up times of 7.1 months (interquartile range,

15.1 months) and 3.6 months (interquartile range, 5.7 months) for Brigham and Women's Hospital and Tulane University Medical Center, respectively ($p = 0.0043$) (Tables 1 and 2). Patient demographics were comparable between the two institutions, with a predominance of female (Brigham and Women's Hospital, 68 percent; Tulane University Medical Center, 71 percent; $p = 0.74$), middle-aged (average age, Brigham and Women's Hospital, 40 years; Tulane University Medical Center, 42 years; $p = 0.55$), and overweight or obese patients (average body mass index: Brigham and Women's Hospital, 31.7 kg/m^2; Tulane University Medical Center, 33.2 kg/m^2; $p = 0.26$). There was no significant difference in the prevalence of comorbidities, including smoking history, diabetes mellitus, hypertension, polycystic ovarian syndrome, and inflammatory gastrointestinal conditions such as Crohn's disease. Although there was no difference in the proportion of patients who had a history of systemic pharmacologic management before their first excisional operation during this study period (Brigham and Women's Hospital, 85 percent; Tulane University Medical Center, 86 percent; $p = 0.91$), patients in the Tulane University Medical Center cohort were more likely to have been treated with biologics (Brigham and Women's Hospital, 27 percent; Tulane University Medical Center, 47 percent; $p = 0.041$) and immunosuppressants such as methotrexate (Brigham and Women's Hospital, 5 percent; Tulane University Medical Center, 53 percent; $p < 0.0001$), and patients in the Brigham and Women's Hospital cohort were more likely to have been treated with steroids (Brigham and Women's Hospital, 40 percent; Tulane University Medical Center, 17 percent; $p = 0.012$) (Table 1).

Operative Characteristics

The treatment episodes involved a total of 447 and 101 excisional sites in the Brigham and Women's Hospital and Tulane University Medical Center cohorts, respectively, with largely comparable proportions of anatomical areas, with the axilla as the most common site (Brigham and Women's Hospital, 33 percent; Tulane University Medical Center, 34 percent; $p = 0.73$), followed by the perineum and groin/thighs, with the buttocks significantly more common in the Tulane University Medical Center cohort (Brigham and Women's Hospital, 6 percent; Tulane University Medical Center, 13 percent; $p = 0.01$). Approximately half of the episodes were completed as day surgical procedures (Brigham and Women's Hospital, 49 percent; Tulane University Medical Center, 64 percent; $p = 0.06$). For those that required hospitalization, the average length of stay was 4.0 days (Table 2). Four categories of treatment episodes were identified based on their timing and technique of postexcisional wound closure: immediate closure [closure of all wounds immediately following excision in the same operation (61 percent of all episodes)], accelerated delayed closure [temporary closure of excisional wound over negative-pressure wound therapy device with subsequent definitive closure in a second operation during the same hospitalization (35 percent of all Brigham and Women's Hospital episodes)], wick-assisted closure [immediate closure of wound with small iodoform gauze wicks placed between sutures for fluid removal (45 percent of all Tulane University Medical Center episodes)], or healing by secondary intention [wounds left open with serial dressing changes (13 percent of all Tulane University

Table 1. Patient Demographics*

	Combined (%)	BWH (%)	TUMC (%)	*p*
No. of patients	181	146	35	
Sex				
Male	56/181 (31)	46/146 (32)	10/35 (29)	
Female	125/181 (69)	100/146 (68)	25/35 (71)	NS
Mean age ± SD, yr	40 ± 14	40 ± 14	42 ±14	NS
Mean BMI ± SD, kg/m^2	31.9 ± 7.6	31.7 ± 7.4	33.2 ±8.7	NS
Smoking history	80/180 (44)	62/146 (42)	18/35 (51)	NS
Diabetes mellitus	34/180 (19)	30/146 (21)	4/35 (11)	NS
Hypertension	41/180 (23)	30/146 (21)	11/35 (31)	NS
Inflammatory GI conditions	11/180 (6)	10/146 (7)	1/35 (3)	NS
PCOS	14/125 (11)	13/100 (13)	1/25 (4)	NS
History of medical therapy	154/180 (85)	124/146 (85)	30/35 (86)	NS
Antibiotics	136/154 (88)	113/124 (90)	23/30 (77)	NS
Biologics	48/154 (31)	34/124 (27)	14/30 (47)	0.041
Steroids	56/154 (36)	51/124 (40)	5/30 (17)	0.012
Hormone blockers	28/154 (18)	24/124 (19)	4/30 (13)	NS
Immunosuppressants	22/154 (14)	6/124 (5)	16/30 (53)	<0.0001

BWH, Brigham and Women's Hospital; TUMC, Tulane University Medical Center; NS, not statistically significant; BMI, body mass index; GI, gastrointestinal; PCOS, polycystic ovarian syndrome.
*Continuous variables expressed as mean ± SD.

Table 2. Operative Characteristics*

	Combined (%)	BWH (%)	TUMC (%)	*p*
Operative cases	435	385	50	—
Treatment episodes	316	269	47	—
Immediate closure (I)	193/316 (61)	176/269 (65)	17/47 (36)	—
Accelerated delayed closure (A)	93/316 (29)	93/269 (35)	0/47 (0)	—
Wick-assisted closure (W)	21/316 (7)	0/269 (0)	21/47 (45)	—
Secondary healing (S)	6/316 (2)	0/269 (0)	6/147 (13)	—
Other delayed closure (D)	3/316 (1)	0/269 (0)	3/147 (6)	—
Follow-up time, mo*				0.0043
Median	6.8	7.1	3.6	
Interquartile range	13.5	15.1	35.7	
Mean length of hospitalization ± SD, days	4.0 ± 3.0	4.1 ± 2.8	4.2 ± 3.9	NS
Excisional sites	548	447	101	—
Axilla	182/548 (33)	147/447 (33)	35/101 (34)	NS
Perineum	111/548 (20)	94/447 (21)	17/101 (17)	NS
Groin/thigh	110/548 (20)	91/447 (20)	19/101 (19)	NS
Buttocks	39/548 (7)	26/447 (6)	13/101 (13)	0.01
Breast/chest	31/548 (6)	27/447 (6)	4/101 (4)	NS
Penoscrotal	31/548 (6)	25/447 (6)	6/101 (6)	NS
Abdomen	28/548 (5)	22/447 (5)	6/101 (6)	NS
Scalp/face/neck	16/548 (3)	15/447 (3)	1/101 (1)	NS
Episodes involving flap closure	44/316 (14)	12/269 (4)	32/47 (68)	<0.0001
Episodes involving skin grafts	37/316 (12)	27/269 (10)	10/47 (21)	0.03
Conventional graft (STSG, FTSG)	26/37 (70)	18/27 (67)	8/10 (80)	—
Recycled graft	9/37 (24)	9/27 (33)	0/10 (0)	—
Skin substitute graft	2/37 (6)	0/27 (0)	2/10 (20)	—
NPWT placed over graft	24/37 (65)	19/27 (70)	5/10 (50)	—

BWH, Brigham and Women's Hospital; TUMC, Tulane University Medical Center; NS, not statistically significant; STSG, split-thickness skin graft; FTSG, full-thickness skin graft; NPWT, negative-pressure wound therapy.
*Expressed as median and interquartile range; all other continuous variables expressed as mean ± SD.

Medical Center episodes)]. A fifth category, other delayed closure, encompassed three episodes of staged closure from the Tulane University Medical Center cohort that did not qualify for the above categories (Table 2 and Fig. 2). The details of these unique approaches are discussed in detail below. In addition, although the Tulane University Medical Center cohort involved significantly more episodes using flap closure (Brigham and Women's Hospital, 4 percent; Tulane University Medical Center, 68 percent; $p < 0.0001$) and skin grafts (Brigham and Women's Hospital, 10 percent; Tulane University Medical Center, 21 percent; $p = 0.03$), only the Brigham and Women's Hospital cohort used recycled skin grafts, or grafts harvested from a diseased donor site, eradicated of affected subcutaneous tissue, and applied to the excised area.

Accelerated Delayed Closure

All delayed closure episodes in the Brigham and Women's Hospital cohort used a method coined "accelerated delayed closure," in which the surgeon largely closes the defect over the polyurethane foam, then returns to the operating room after 2 to 4 days of negative-pressure wound therapy for definitive closure. Here, we present a representative case of a 17-year-old male patient with severe bilateral axillary hidradenitis, who was treated with wide local excision, local tissue rearrangement, and application of negative-pressure wound therapy with suction pressure of 125 mmHg (Fig. 3). After 2 days, the foam was removed intraoperatively and closure achieved through unmeshed split-thickness skin grafts harvested from the right anterolateral thigh. Here, negative-pressure wound therapy was applied over the split-thickness skin grafts, ultimately achieving excellent graft take, sustained healing, and no local recurrences at 29 months. We further feature a case of a 24-year-old female patient with severe perineal hidradenitis, who underwent local excision of 180 cm^2 and application of a moisture-retentive hydrocolloid dressing overlaid with negative-pressure wound therapy (Fig. 4). She underwent definitive primary closure 3 days afterward, with excellent healing noted at 24 months.

Wick-Assisted Closure

The Tulane University Medical Center cohort used a single-stage method combining immediate closure and the use of iodoform gauze strips, or wicks, to facilitate fluid removal and wound optimization. Skin flaps were raised following excision, allowing for low-tension suture closure with small intervening spaces, through which half-inch iodoform gauze wick

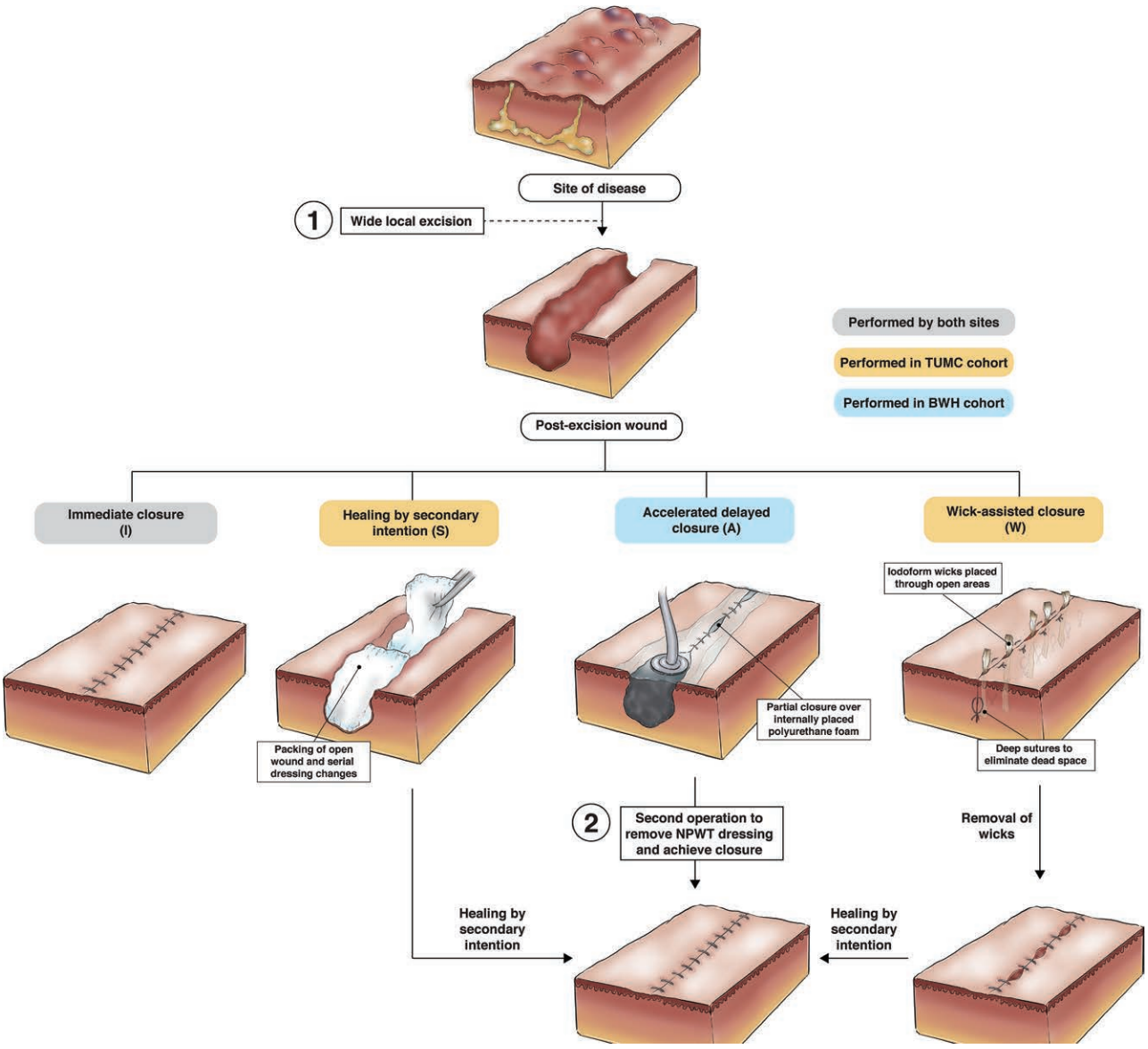


Fig. 2. Approaches to closure following wide local excision of hidradenitis suppurativa. Treatment episodes across two geographically disparate academic centers were classified based on unique closure techniques. This included immediate closure (*I*) (closure of all wounds immediately following excision in same operation), healing by secondary intention (*S*) (wounds left open with serial dressing changes), wick-assisted closure (*W*) (immediate closure of wound with small iodoform gauze wicks placed between sutures for fluid removal), and accelerated delayed closure (*A*) (temporary closure of excisional wound over negative-pressure wound therapy device with subsequent definitive closure in a second operation during the same hospitalization). Three episodes in the Tulane University Medical Center cohort were classified as other delayed closure (not shown) and represented staged closure techniques that did not conform to the above categories. *BWH*, Brigham and Women's Hospital; *TUMC*, Tulane University Medical Center; *NPWT*, negative-pressure wound therapy.

strips could be threaded to reach the base of the wound cavity. The iodoform gauze strips were removed at the first postoperative visit, typically 1 week after surgery. Here, we show a representative case of a 37-year old female patient with a 20-year history of Hurley stage III right axillary hidradenitis, compounded by severe macromastia causing tethering of her scar and axillary tissue (Fig. 5). After performing a wide local excision encompassing the entire hair-bearing axilla, a 6-cm backcut was created on the lateral chest wall to mobilize a fasciocutaneous rotation advancement flap. Placing an ovine forestomach matrix graft over exposed vessels and the pectoralis major muscle, the flap was advanced to the midline and closed, with intervening iodoform

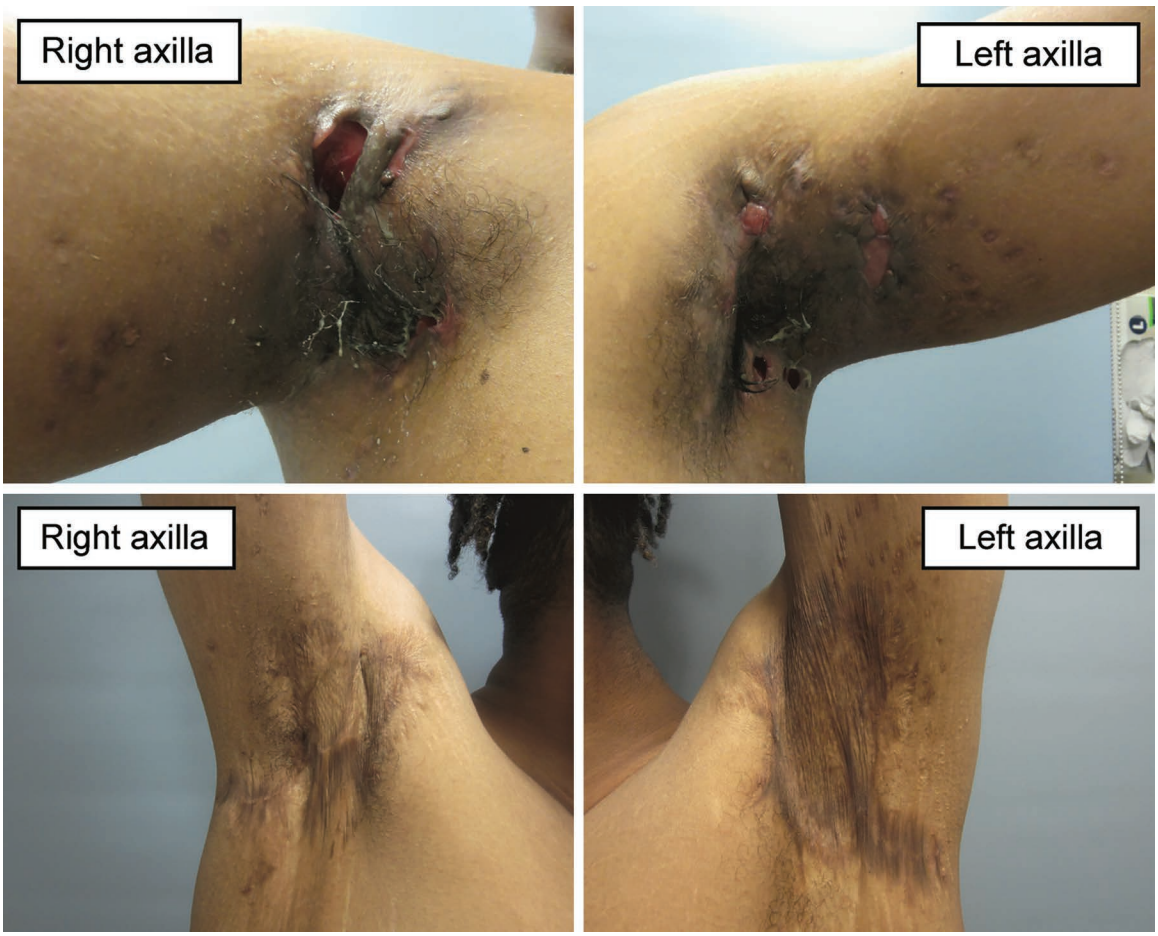


Fig. 3. Example of treatment of axillary hidradenitis suppurativa with accelerated delayed closure using negative-pressure wound therapy. (*Above*) Preoperative images of bilateral axillary hidradenitis suppurativa. (*Below*) Postoperative images at 29 months show sustained healing and no local recurrences.

gauze strips placed between pledgeted retention sutures. Complete wound closure was observed at 2 months, with no local recurrence and full range of motion of her right upper extremity. [**See Video (online)**, which shows an interview with a patient following wide local excision of severe axillary hidradenitis suppurativa. One of the authors (A.E.C.) interviews a female patient about her experience with hidradenitis suppurativa, her excisional procedure with wick-assisted closure, and the impact of surgical intervention on her quality of life.]

Other Delayed Closure

Three episodes from the Tulane University Medical Center cohort used staged closure methods that did not conform to the four established categories. This included two episodes involving skin graft–based coverage 3 to 4 days following excision and placement of a negative-pressure wound therapy device on either open or partially open excisional wounds. The third involved a patient with severe hidradenitis suppurativa of the abdominal, bilateral thigh, and perineal region, whose excisional wounds were left open with serial dressing changes before flap and skin graft–based closure after 3 days.

Recycled Skin Grafts

Of the 27 Brigham and Women's Hospital episodes involving skin grafts, 33 percent of these involved recycled skin grafting, where grafts are harvested from diseased areas and thinned to include only the healthy surface superficial to the folliculosebaceous units. We show representative photographs from a 24-year old patient with hidradenitis of the posterior scalp (Fig. 6), whose excision was closed using a recycled split-thickness skin graft and an overlying negative-pressure wound therapy device. His surgical site was noted to have wound closure and sustained healing at 10 months postoperatively.

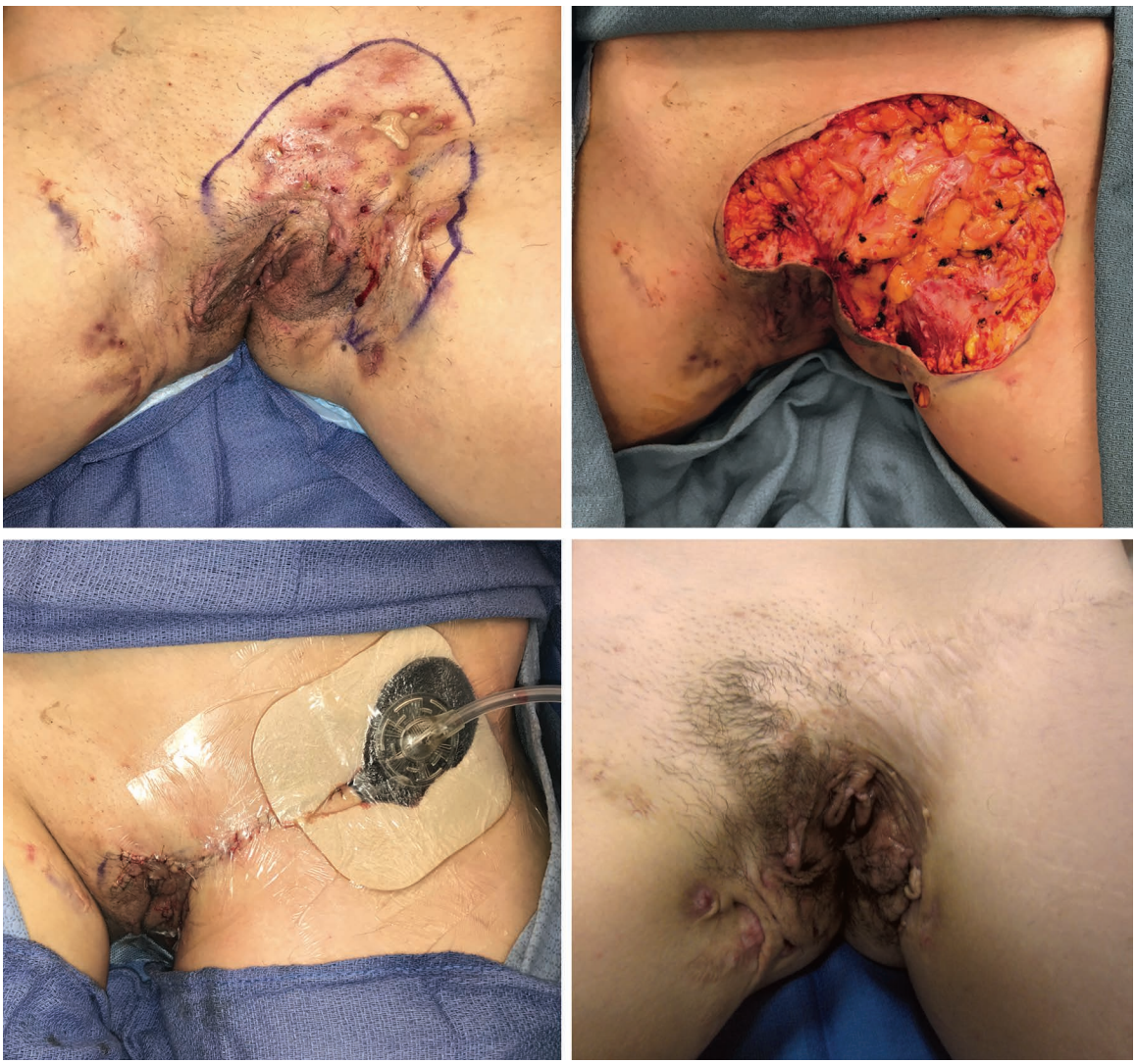


Fig. 4. Example of treatment of perineal hidradenitis suppurativa with accelerated delayed closure using negative-pressure wound therapy. (*Above*, *left*) Preoperative image of severe perineal hidradenitis suppurativa. (*Above*, *right*) Following wide local excision of the affected area, the patient underwent accelerated delayed closure with (*below*, *left*) negative-pressure wound therapy and definitive closure of the wound in a single hospitalization. Postoperative image shows sustained healing at 24 months (*below*, *right*).

Outcomes and Complications

Overall, 94 percent of episodes across the two sites achieved healing, with a median healing time of 3.0 months (interquartile range, 4.2 months), despite encompassing extensive operations with an average excisional area of 152 cm^2 and over 50 percent of episodes involving multisite excisions. Overall, 36 percent of episodes across the sites achieved healing within 2 months and were included in the study as exceptions to the minimum follow-up period (2 months following surgery). As a supplementary data point, the average percentage closure [calculated as (area left open − total excisional area)total excisional area × 100] was 99 percent across all patients with complete area data. Twenty percent of episodes required reoperation at the same site during the study period for new or progressing disease. 51 percent of episodes encountered at least one complication during the postoperative 30-day period, with delayed healing (dehiscence or any other open area noted on clinical examination) as the most common, and constituted 65 percent of all documented complications (Table 3). Examining the 11 patients among the Brigham and Women's Hospital cohort who were documented to be unhealed at the final follow-up, the vast majority involved Hurley stage III disease, with many

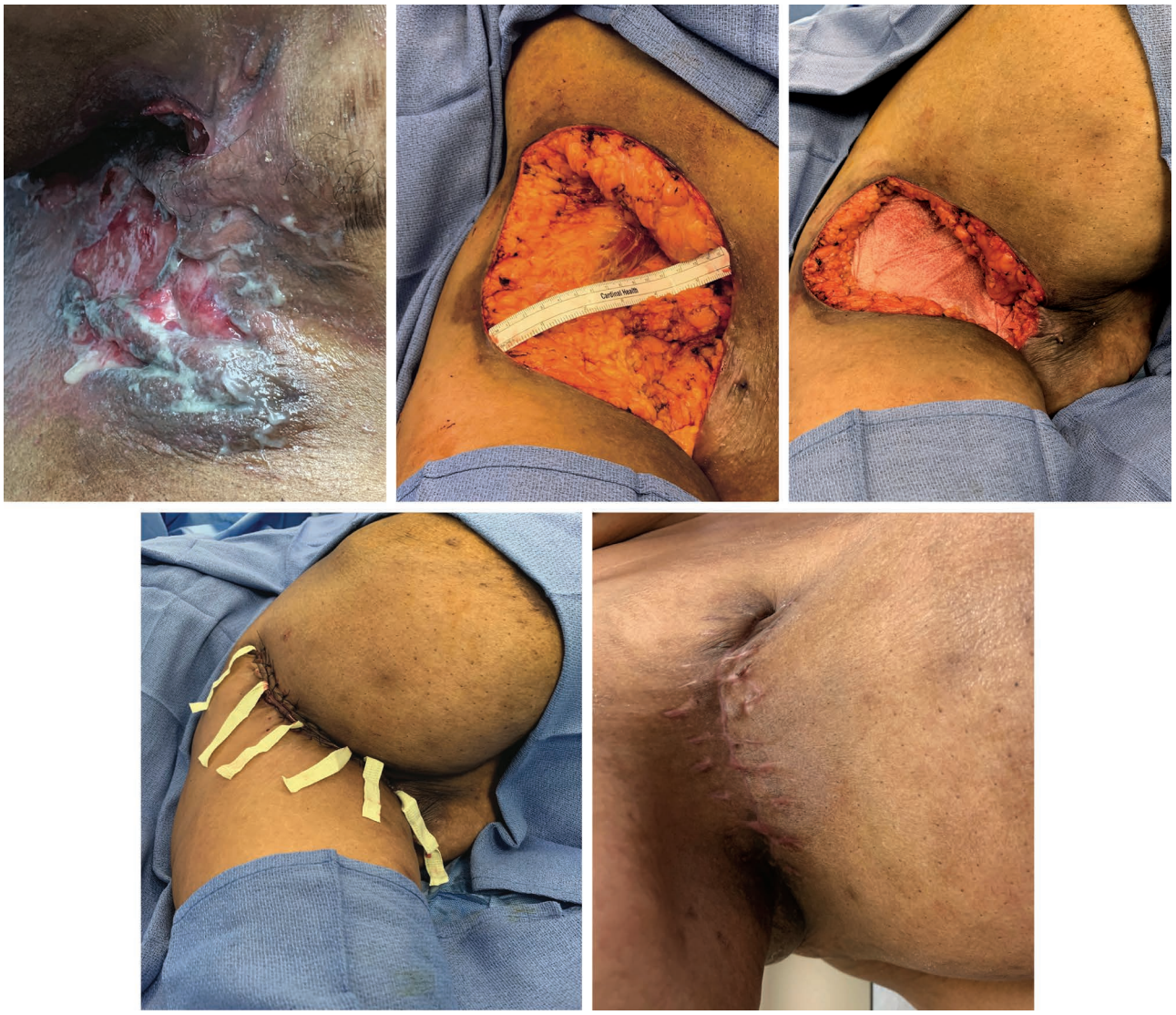


Fig. 5. Example of wick-assisted closure following wide local excision. (*Above*, *left*) Preoperative image of hidradenitis suppurativa lesion showing severe axillary disease. (*Above*, *center*) Intraoperative image of defect following wide excision. (*Above*, *right*) Placement of ovine forestomach matrix graft in the wound bed. (*Below*, *left*) Closure using fasciocutaneous rotation advancement flaps and iodoform gauze wicks and retention sutures. (*Below*, *right*) Postoperative image shows complete healing at 2 months.

harboring comorbidities, including overweight and obese status, history of smoking, and diabetes. (**See Table, Supplemental Digital Content 1**, which shows the patient courses with unhealed wounds at final follow-up. *BWH*, Brigham and Women's Hospital, ***http://links.lww.com/PRS/F432***.)

When juxtaposing the two clinical sites, the Tulane University Medical Center cohort involved significantly more extensive excisions (Brigham and Women's Hospital, 151 cm^2; Tulane University Medical Center, 261 cm^2; $p = 0.0003$), with a lower healing rate than Brigham and Women's Hospital (Brigham and Women's Hospital, 95 percent; Tulane University Medical Center, 85 percent; $p = 0.017$) but with no difference in rate of local reoperations (Brigham and Women's Hospital, 21 percent; Tulane University Medical Center, 13 percent; $p = 0.18$) or postoperative complications (Brigham and Women's Hospital, 52 percent; Tulane University Medical Center, 45 percent; $p = 0.33$). There was no difference in the overall healing time, with median healing times of 3.0 months (interquartile range, 4.1 months) and 2.5 months (interquartile range, 4.4 months) for Brigham and Women's Hospital and Tulane University Medical Center, respectively ($p = 0.86$) (Table 3).

Examining immediate closure and accelerated delayed closure episodes at Brigham and

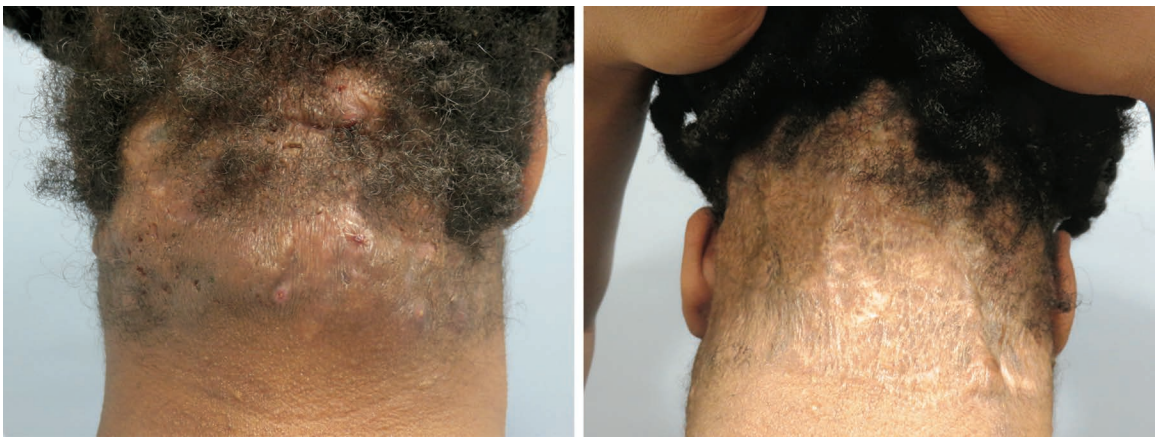


Fig. 6. Example of treatment with recycled skin grafts for closure following wide local excision. (*Left*) Patient with hidradenitis of the posterior scalp, undergoing excision and closure using recycled skin grafts. (*Right*) Postoperative image captures the surgical site with complete wound closure and sustained healing at 10 months.

Women's Hospital, the accelerated delayed closure episodes were characterized by greater excisional area (immediate closure, 94 cm^2; accelerated delayed closure, 257 cm^2; $p < 0.0001$), lower rate of complete healing (immediate closure, 98 percent; accelerated delayed closure, 90 percent; $p = 0.01$), longer healing time (immediate closure, 3.4 months; accelerated delayed closure, 6.5 months; $p = 0.0001$), and greater proportion of episodes involving multisite excisions (immediate closure, 34 percent; accelerated delayed closure, 76 percent; $p < 0.0001$) and postoperative complications (immediate closure, 42 percent; accelerated delayed closure, 72 percent; $p < 0.0001$). However, there was no significant difference in the proportion of episodes requiring local reoperation (immediate closure, 17 percent; accelerated delayed closure, 27 percent; $p = 0.06$). [**See Table, Supplemental Digital Content 2**, which shows site-specific outcomes (Brigham and Women's Hospital), ***http://links.lww.com/PRS/F433***.] As two variants of closures performed alongside the initial excision, immediate and wick-assisted closures in the Tulane University Medical Center cohort were comparable in every parameter, including excisional area (immediate closure, 272 cm^2; wick-assisted closure, 273 cm^2; $p = 0.99$), proportions of multisite excisions (immediate closure, 65 percent; wick-assisted closure, 52 percent; $p = 0.44$), rate of complete healing (immediate closure, 88 percent; wick-assisted closure, 86 percent; $p > 0.99$), total healing time (immediate closure,

Table 3. Combined Site Outcomes

	Combined (%)	BWH (%)	TUMC (%)	*p*
Treatment episodes with follow-up	316	269	47	—
Total excisional area ± SD, cm^2	152 ± 142	151 ± 175	261 ± 245	0.0003
≥2 excisional sites	166/316 (53)	136/269 (51)	30/47 (64)	NS
Healing achieved?	296/316 (94)	256/269 (95)	40/47 (85)	0.017
Total healing time, mo*				NS
Median	3.0	3.0	2.5	
Interquartile range	4.2	4.1	4.4	
Episodes requiring reoperation at local site	63/316 (20)	57/269 (21)	6/47 (13)	NS
Episodes with postoperative complications	162/316 (51)	141/269 (52)	21/47 (45)	NS
30-day complications	184	158	26	
Delayed healing	119/184 (65)	110/158 (70)	9/26 (34)	—
Infection	12/184 (6)	7/158 (4)	5/26 (19)	—
New disease at local site	9/184 (5)	7/158 (4)	2/26 (8)	—
Hypertrophic granulation tissue	7/184 (4)	7/158 (4)	0/26 (0)	—
Bleeding	6/184 (3)	6/158 (4)	0/26 (0)	—
Other	6/184 (3)	4/158 (3)	2/26 (8)	—
Seroma/hematoma	5/184 (3)	4/158 (3)	1/26 (4)	—
Failed healing	19/184 (10)	13/158 (8)	7/26 (27)	—

BWH, Brigham and Women's Hospital; TUMC, Tulane University Medical Center; NS, not statistically significant; STSG, split-thickness skin graft; FTSG, full-thickness skin graft; NPWT, negative-pressure wound therapy.
*Expressed as median and interquartile range; all other continuous variables expressed as mean ± SD.

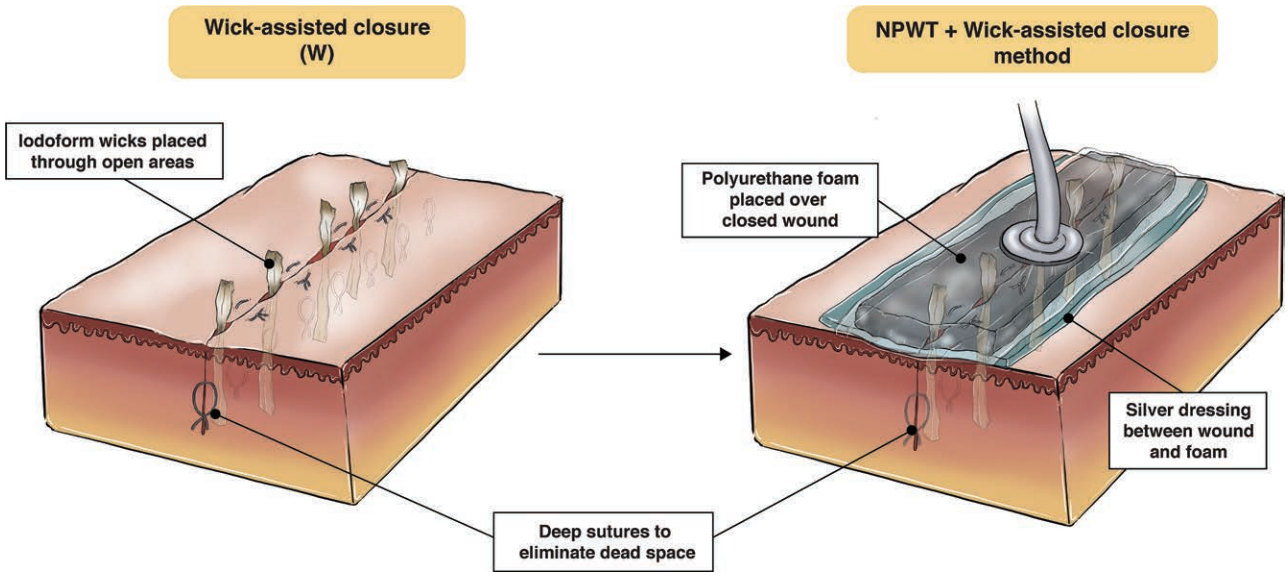


Fig. 7. Incorporation of negative-pressure wound therapy (*NPWT*) technique into wick-assisted closure (*W*). Illustration of newly evolved method, with addition of overlying silver antimicrobial wound contact layer and negative-pressure wound therapy device over closed wound with intervening iodoform gauze wicks.

4.0 months; wick-assisted closure, 4.8 months; $p = 0.73$), and number of episodes requiring local reoperations (immediate closure, 6 percent; wick-assisted closure, 10 percent; $p > 0.99$) and with postoperative complications (immediate closure, 47 percent; wick-assisted closure, 43 percent; $p = 0.80$). [**See Table, Supplemental Digital Content 3**, which shows site-specific outcomes (Tulane University Medical Center), ***http://links.lww.com/PRS/F434***.]

DISCUSSION

In this multi-institutional retrospective study, we demonstrate that surgery is an effective treatment for patients with moderate and severe hidradenitis suppurativa. Although the rate of complications was high in the 30-day postoperative period, delayed healing constituted the majority and was managed through conservative wound care.

Despite largely comparable patient and operative characteristics, this work captured various site-specific surgical modalities for the common goal of accelerating time to closure and healing. Notably, the Brigham and Women's Hospital group used a two-stage accelerated delayed closure technique with internal negative-pressure wound therapy bridging the initial excision and definitive closure. This technique achieved good outcomes, with 90 percent of episodes with complete healing, albeit lower than the immediate closure counterparts—a disparity that is likely at least partially attributable to more extensive disease in the delayed group. Although further studies are required to better elucidate precise indications for this approach, these data suggest that single-hospitalization, staged closure using internal negative-pressure wound therapy may be a viable and safe option for large, multisite excisions.

The Tulane University Medical Center group supplemented their conventional immediate closures with iodoform gauze wicks to reduce fluid accumulation and to optimize the wound following discharge. Although limited by relatively small sample size, episodes for these two approaches achieved over 85 percent healing and were comparable across all outcomes studied. For all techniques highlighted, further investigation of the risks, benefits and long-term outcomes, including but not limited to patient-reported satisfaction levels and rate of postoperative narcotic use, will be paramount in establishing clinical algorithms for the optimal treatments tailored to the disease profile of each patient.

Finally, this study was instrumental in opening avenues for collaborative development of new combined techniques. Although not captured in this case series, the heavy use of negative-pressure wound therapy in the Brigham and Women's Hospital cohort inspired the Tulane University Medical Center authors to develop a new wick-assisted closure method, where a conventional

negative-pressure wound therapy device is placed over the closure and iodoform wicks with an intervening antimicrobial silver wound contact layer. This combined method is designed to further accelerate fluid evacuation in wounds amenable to immediate closure—a testament to the evolving nature of this field and the potential for innovation through the active exchange of intellectual capital and surgical craft (Fig. 7).

There are several limitations to this study, including its retrospective nature, relatively short follow-up time in certain patients, and the focus on patients treated in academic tertiary care facilities, potentially limiting the generalizability to broader populations of hidradenitis suppurativa patients across geographic and socioeconomic boundaries. Meaningful comparisons between the outcomes of individual treatment modalities discussed are limited, given that defect size, disease severity, and patient comorbidities invariably dictate the surgeon's choice of approach. Furthermore, this study captures only a limited sample of previously described reconstructive surgical options, although we have identified several unique and site-specific approaches, including the interval placement of iodoform wicks to enhance fluid removal and the use of full-thickness skin grafts beyond the gluteal and perianal region.

Surgery serves as an effective and safe option for hidradenitis suppurativa, particularly amidst a global pandemic that confers additional risk to pharmacologic options that are immunosuppressive or require frequent trips to health care facilities. This work captures several techniques that may be customized to each patient and underscores the importance of early involvement of experienced plastic surgeons, particularly for patients with comorbidities that compromise wound healing or severe disease that limits tissue availability for reconstruction. Hidradenitis suppurativa demands close collaboration with adjunct subspecialties, including dermatology, gynecology, urology, and colorectal surgery, and although not specifically investigated in this work, strategies to improve multidisciplinary care remain a topic for further research. Although establishing indications for these procedures is beyond the scope of this study, we believe that large retrospective studies such as our own are an important step toward future studies that may elucidate further data to make evidence-based guidelines a reality. Perhaps most importantly, this two-institution effort highlights the importance of intradisciplinary collaboration as we strive to establish evidence-based clinical recommendations for optimal surgical management of this highly challenging condition.

Dennis P. Orgill, M.D., Ph.D.
Division of Plastic Surgery
Brigham & Women's Hospital
75 Francis Street
Boston, Mass. 02115
dorgill@bwh.harvard.edu
Instagram: @ryoko_hamaguchi, @ryokohamaguchimd
Twitter: @RyokoHamaguchi

PATIENT CONSENT

Patients provided written informed consent for the use of their images.

ACKNOWLEDGMENT

The authors express their gratitude to the late Ralph E. Newsome, Jr., M.D., whose operative cases were included in the Tulane University Medical Center cohort and were invaluable in realizing this study.

REFERENCES

1. Ingram JR, Collier F, Brown D, et al. British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. *Br J Dermatol.* 2019;180:1009–1017.
2. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part I: Diagnosis, evaluation, and the use of complementary and procedural management. *J Am Acad Dermatol.* 2019;81:76–90.
3. Hurley H. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa and familial benign pemphigus: Surgical approach. In: *Dermatologic Surgery: Principles and Practice.* 2nd ed. New York: Dekker; 1996:623–645.
4. Robert E, Bodin F, Paul C, et al. Non-surgical treatments for hidradenitis suppurativa: A systematic review. *Ann Chir Plast Esthet.* 2017;62:274–294.
5. Ritz JP, Runkel N, Haier J, Buhr HJ. Extent of surgery and recurrence rate of hidradenitis suppurativa. *Int J Colorectal Dis.* 1998;13:164–168.
6. Balik E, Eren T, Bulut T, Büyükuncu Y, Bugra D, Yamaner S. Surgical approach to extensive hidradenitis suppurativa in the perineal/perianal and gluteal regions. *World J Surg.* 2009;33:481–487.
7. Kishi K, Nakajima H, Imanishi N. Reconstruction of skin defects after resection of severe gluteal hidradenitis suppurativa with fasciocutaneous flaps. *J Plast Reconstr Aesthet Surg.* 2009;62:800–805.
8. Unal C, Yirmibesoglu OA, Ozdemir J, Hasdemir M. Superior and inferior gluteal artery perforator flaps in reconstruction of gluteal and perianal/perineal hidradenitis suppurativa lesions. *Microsurgery* 2011;31:539–544.
9. Wormald JC, Balzano A, Clibbon JJ, Figus A. Surgical treatment of severe hidradenitis suppurativa of the axilla: Thoracodorsal artery perforator (TDAP) flap versus split skin graft. *J Plast Reconstr Aesthet Surg.* 2014;67:1118–1124.

10. Chen YE, Gerstle T, Verma K, Treiser MD, Kimball AB, Orgill DP. Management of hidradenitis suppurativa wounds with an internal vacuum-assisted closure device. *Plast Reconstr Surg.* 2014;133:370e–377e.
11. Honda T, Tachibana T, Kitoh A, Morita K, Onodera H, Miyachi Y. A case of chronic perianal pyoderma treated with the recycled skin graft method. *J Dermatol.* 2002;29:96–99.
12. Kuo HW, Ohara K. Surgical treatment of chronic gluteal hidradenitis suppurativa: Reused skin graft technique. *Dermatol Surg.* 2003;29:173–178.
13. Maeda T, Kimura C, Murao N, Takahashi K. Promising long-term outcomes of the reused skin-graft technique for chronic gluteal hidradenitis suppurativa. *J Plast Reconstr Aesthet Surg.* 2015;68:1268–1275.
14. Ovadja ZN, Bartelink SAW, van de Kar AL, van der Horst CMAM, Lapid O. A multicenter comparison of reconstruction strategies after wide excision for severe axillary hidradenitis suppurativa. *Plast Reconstr Surg Glob Open* 2019;7:e2361.
15. Ngaage LM, Wu Y, Ge S, et al. Factors influencing the local cure rate of hidradenitis suppurativa following wide local excision. *Int Wound J.* 2020;17:117–123.
16. Mandal A, Watson J. Experience with different treatment modules in hidradenitis suppurativa: A study of 106 cases. *Surgeon* 2005;3:23–26.
17. Kohorst JJ, Baum CL, Otley CC, et al. Surgical management of hidradenitis suppurativa: Outcomes of 590 consecutive patients. *Dermatol Surg.* 2016;42:1030–1040.
18. Ruan QZ, Chen AD, Singhal D, Lee BT, Fukudome EY. Surgical management of hidradenitis suppurativa: Procedural trends and risk factors. *J Surg Res.* 2018;229:200–207.
19. Worden A, Yoho DJ, Houin H, et al. Factors affecting healing in the treatment of hidradenitis suppurativa. *Ann Plast Surg.* 2020;84:436–440.
20. Burney RE. 35-year experience with surgical treatment of hidradenitis suppurativa. *World J Surg.* 2017;41:2723–2730.

Techniques in Coloproctology
https://doi.org/10.1007/s10151-023-02809-y

TECHNICAL NOTE

Surgical management of perianal fistula using an ovine forestomach matrix implant

A. Hsu[1] · K. Schlidt[2] · C. R. D'Adamo[2] · B. A. Bosque[3] · S. G. Dowling[3] · J. H. Wolf[1,4]

Received: 21 February 2023 / Accepted: 19 April 2023

Abstract

Purpose Invasive surgical management of cryptoglandular perianal fistulas (PF) is challenging because of high recurrence rates and the potential for injury to the sphincter complex. In the present technical note, we introduce a minimally invasive treatment for PF using a perianal fistula implant (PAFI) comprising ovine forestomach matrix (OFM).

Methods This retrospective observational case series highlights 14 patients who had undergone a PAFI procedure at a single center between 2020 and 2023. During the procedure, previously deployed setons were removed and tracts were de-epithelialized with curettage. OFM was rehydrated, rolled, passed through the debrided tract, and secured in place at both openings with absorbable suture. Primary outcome was fistula healing at 8 weeks, and secondary outcomes included recurrence or postoperative adverse events.

Results Fourteen patients underwent PAFI using OFM with a mean follow-up period of 37.6 ± 20.1 weeks. In follow-up, 64% ($n = 9/14$) had complete healing at 8 weeks and all remained healed, except one at last follow-up visit. Two patients underwent a second PAFI procedure and were healed with no recurrence at the last follow-up visit. Of all patients that healed during the study period ($n = 11$), the median time to healing was 3.6 (IQR 2.9–6.0) weeks. No postprocedural infections nor adverse events were noted.

Conclusions The minimally invasive OFM-based PAFI technique for PF treatment was demonstrated to be a safe and feasible option for patients with trans-sphincteric PF of cryptoglandular origin.

Keywords Ovine forestomach matrix · Anal fistula · Perianal fistulas · Extracellular matrix · Fistula plug

Introduction

Surgical management of cryptoglandular perianal fistulas (PF) is challenging because of high recurrence rates and the potential for injury to the sphincter complex [1]. Invasive procedures, such as ligation of intersphincteric fistula tract (LIFT) or mucosal advancements flaps, can offer greater clinical efficacy in comparison to less invasive methods, such as fibrin glue injection. There is a trade-off, however, in that more invasive methods also carry an increased risk of postoperative complications, including infection, bleeding, or anal sphincter damage [2]. Efforts to develop less-invasive methods with higher efficacy have included techniques such as video-assisted anal fistula treatment (VAAFT), fistula laser closure (FiLaC), and stem cell therapy [3]. While promising, these more contemporary options have their own unique challenges, e.g., high capital equipment cost, limited access to training opportunities, or complex programmatic needs for autologous stem cell transplantation [4].

In addressing PF closure, a need still exists for a minimally invasive and clinically efficacious alternate to traditional surgical interventions, which has led to investigations using regenerative biomaterials [1]. Biological implant materials, typically derived from animal or human tissues, have seen adoption in PF treatment [1]. Typically, these types of devices are used as a "fistula plug" to occlude openings to the fistula and are considered less invasive than traditional surgical approaches. However, while biomaterial-based

✉ J. H. Wolf
joswolf@lifebridgehealth.org

1 Department of Surgery, Sinai Hospital, Baltimore, MD, USA

2 University of Maryland School of Medicine, Baltimore, MD, USA

3 Aroa Biosurgery Limited, Auckland, New Zealand

4 Department of Surgery, George Washington University, Washington, D.C., USA

Published online: 03 May 2023

fistula plugs have low patient risk, they also have traditionally demonstrated relatively low clinical efficacy when compared to invasive flap procedures [1]. The ideal biomaterial to serve as a fistula implant must tolerate bacterial contamination and counter local tissue inflammation. This led the authors to postulate that ovine forestomach matrix (OFM) may serve as a suitable biomaterial for this unique application on the basis of existing usage in a range of highly inflamed, irregular, and contaminated wound beds [5]. OFM is a decellularized extracellular matrix (dECM) biomaterial developed for a range of soft tissue repair, reconstruction, and wound healing applications. Once implanted OFM is fully bio-absorbed into the patients regenerating soft tissue and remodeled to leave only functional well-vascularized tissue. OFM-based devices have found utility in the regeneration of contaminated soft tissue defects [5, 6].

To date, there is no reported experience using OFM in PF closure, prompting a single-center retrospective case series to evaluate the use of OFM as a perianal fistula implant (PAFI) to facilitate closure, minimize postoperative complications, and negate the need for more-invasive surgical interventions.

Methods

The study protocol was reviewed by the LifeBridge Health Institutional Review Board, and ethical oversight of the retrospective study was waived. The study was conducted in accordance with institutional guidelines and the World Medical Association Declaration of Helsinki ethical guidelines. All patient information, including any patient images, were de-identified. All patients signed informed consent for the procedure.

Data were collected from patients that met the inclusion/exclusion criteria (Table 1) and represented consecutive patients that had undergone a minimally invasive PAFI using OFM between November 2020 and February 2023. OFM graft (Myriad Matrix Soft Tissue Bioscaffold™, Aroa Biosurgery Limited, Auckland, New Zealand) was used according to the instructions for use. Fistula tracts were not routinely visualized utilizing magnetic resonance imaging (MRI) as part of standard workup but rather were evaluated via physical examination under anesthesia at the time of diagnosis and/or seton placement. All patients were prepared for fistula closure with a non-cutting seton left in place for at least 12 weeks. If the patient was experiencing persistent purulent discharge from the area of the seton, the PAFI device was not utilized as gross infection is a contraindication of this technique and device. Local anesthesia was administered using 1% lidocaine as a bilateral pudendal and circumferential perianal block. The fistula tract was debrided with a curette to remove the epithelial tissue lining the fistulae. The OFM device (5 × 5 cm, 3-layer) was hydrated with saline, then hand rolled to create a cylindrical implant reflecting the length and diameter of the fistula tract (approx. 4–5 cm × 0.3–0.5 cm) (Fig. 1). The OFM implant was secured to the seton with a Vicryl® suture, and when the seton was removed the OFM implant was pulled into the fistula tract. Once passed, the OFM implant was secured internally and externally with approx. 5 mm of overhang using 2–0 Vicryl® suture (Fig. 2). Additional local anesthesia (0.25% bupivacaine or Exparel®) was administered at case conclusion for pain control. No postoperative dressing was applied, but instead patients were instructed to wear surgical underwear. Follow-up visits were conducted at 2 weeks and 8 weeks, for early follow-up, and then 6 and 12 months for long-term follow-up.

Patient demographics (e.g., age, gender, significant baseline comorbidities, Park's classification), prior surgical interventions, and outcomes (e.g., complete healing, recurrence, complications) were captured in Excel (Microsoft Corporation). Significant patient comorbidities included diabetes mellitus, obesity, psychiatric disorders, atrial fibrillation, diverticulosis, irritable bowel syndrome, and illicit drug use. The primary study outcome was defined as complete healing at postoperative week 8. Secondary endpoints included mean time to complete healing, recurrence of fistula during the follow-up interval, and postoperative complications (e.g., infection, pain, and recurrence). Descriptive statistics (e.g., median, interquartile range (IQR), mean, standard deviation (SD)) were computed using GraphPad Prism (version 9.5.0, Dotmatics Inc).

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Male or female patients aged 18 years or above	Patients still under active management having received their anal fistula treatment < 3 months prior
Patients with primary or recurrent anal fistula (cryptoglandular disease) treated with OFM as part of their soft tissue reconstruction procedure	Patients that did not receive OFM as part of their treatment
	Patients with inflammatory bowel disease
	Patients with Crohn's disease
	Patients with acute perianal infection

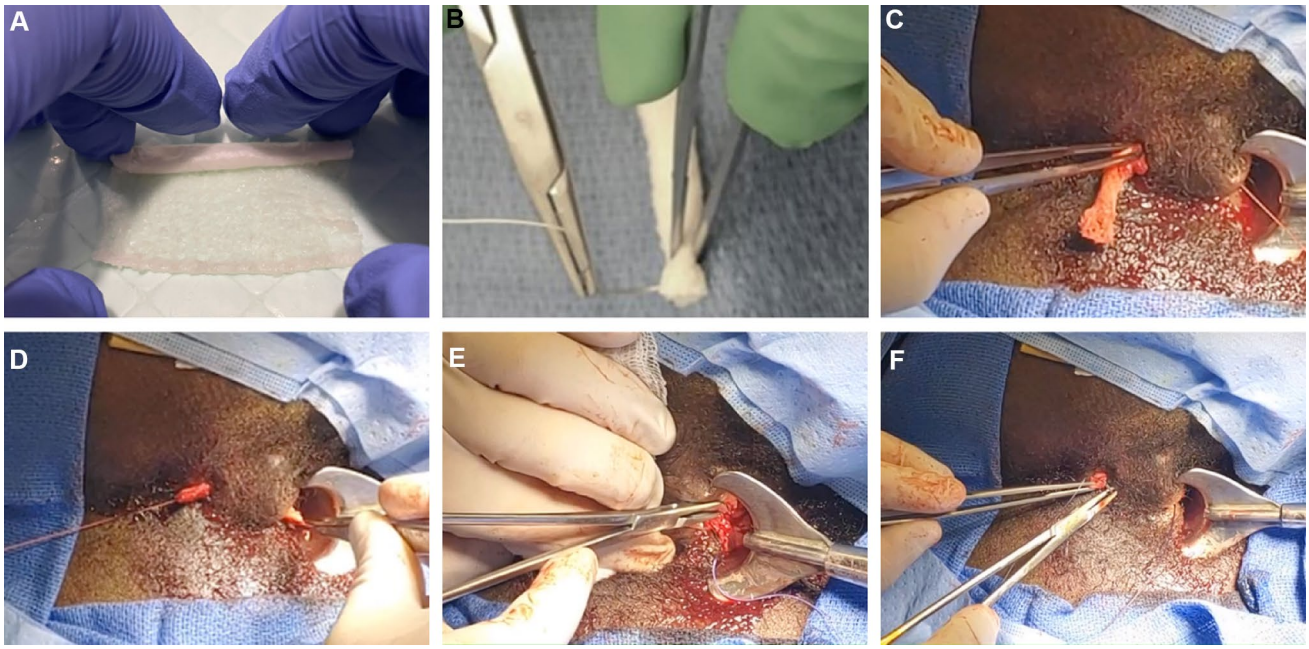


Fig. 1 Representative images of the OFM-based PAFI technique. **a** OFM graft (5×5 cm) rolled to form a cylindrical implant, approx. 5×0.5 cm diameter, then **b** attaching the OFM implant, via suture to the end of a seton. **c** The seton is passed through the PF canal, the OFM implant was drawn through the fistula via the suture aided by forceps. The ends of the OFM implant were then secured internally (**d**) and externally (**e**) with suture

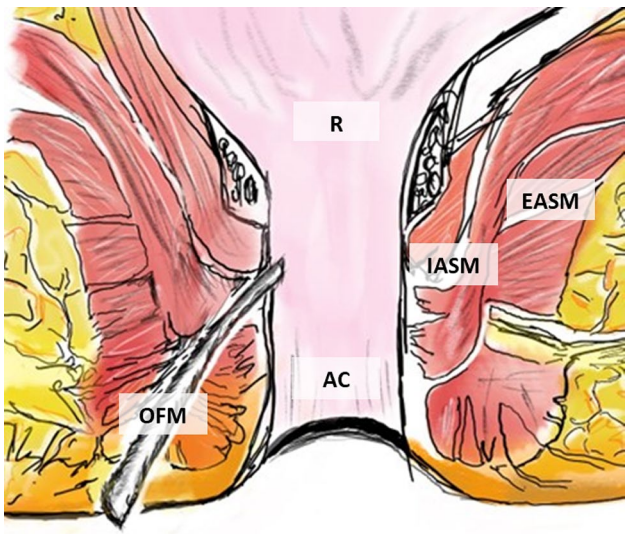


Fig. 2 Schematic representation of the OFM-based PAFI technique. *OFM* ovine forestomach matrix implant, *AC* anal canal, *R* rectum, *IASM* internal anal sphincter muscle, *EASM* external anal sphincter muscle

Results

A total of ten male and four female participants were included in this case series with a mean age of 56.5 ± 16.0 years (Table 2). Eleven participants presented with additional complicating comorbidities (Table 2). All cases were isolated trans-sphincteric PF, except patient #4 who presented with an additional extra-sphincteric PF. The consecutive case series included five cases presenting as a recurrent PF and nine cases as a primary PF, and $n = 3/14$ (21%) cases had undergone a prior surgical intervention (Table 2). The mean length of the PF was 4.0 ± 0.8 cm, and all participants were experiencing preoperative pain associated with their PF.

Of the 14 participants, six (43%) were fully healed at week 4 follow-up visit, and nine (64%) were healed at the week 8 visit (Table 3). The week 8 non-healing patients (#5, #8, #10, and #11) experienced drainage from the PF. Two unhealed patients (#5 and #12) at week 8 underwent a second PAFI procedure, with the fistula noted as healed within 4 weeks following the second procedure in both participants. In the case of patient #5, the re-do PAFI was preceded by seton replacement (12 weeks) to de-escalate the inflammation at the fistula site, which had purulent drainage. Patient #12 did not have purulent drainage and the repeat PAFI was performed without seton replacement. There was no significant fibrosis or scarring noted in either of the cases requiring re-implantation. Patient #14 was healed by week 8, but the fistula had recurred at the time of last follow-up visit. Over the study period a total of

Table 2 Patient demographics and baseline perianal fistula

Patient #	Age (years)	Male/female	Type of PF	Length (cm)	Primary/recurrent	Prior surgical intervention (yes/no)
1	55	M	Trans-sphincteric	4.0	Recurrent	Yes
2	64	F	Trans-sphincteric	4.0	Recurrent	No
3	74	M	Trans-sphincteric	3.0	Primary	No
4	59	M	Trans-sphincteric Extra-sphincteric	6.0	Primary	Yes
5	60	M	Trans-sphincteric	5.0	Primary	No
6	70	F	Trans-sphincteric	4.0	Recurrent	No
7	66	M	Trans-sphincteric	3.5	Recurrent	No
8	55	M	Trans-sphincteric	4.0	Recurrent	Yes
9	71	M	Trans-sphincteric	3.0	Primary	No
10	50	M	Trans-sphincteric	3.0	Primary	No
11	36	F	Trans-sphincteric	4.0	Primary	No
12	33	F	Trans-sphincteric	4.0	Primary	No
13	23	M	Trans-sphincteric	4.0	Primary	No
14	71	M	Trans-sphincteric	4.0	Primary	No
	56.5 ± 16.0 [56.4 (46.5–70.3)]	71%/29%		4.0 ± 0.8 [4.0, (3.4–4.0)]	64%/36%	21%/79%

Errors represent standard deviation of the mean. Median and IQR are included in [], where applicable

Table 3 Study outcomes

Patient #	Outcome at postoperative week 8?	Complications at postoperative week 8?	Postoperative antibiotic use?	Antibiotic duration (days)	Product utilization	Time to heal (weeks)	Last follow-up (weeks)	Recurrence at last follow-up?
1	Healed	None	No	N/A	1	1.6	61.6	No
2	Healed	None	Yes	7	1	3.6	33.3	No
3	Healed	None	No	N/A	1	2.0	42.7	No
4	Healed	None	Yes	7	1	3.3	48.9	No
5	Unhealed	Drainage; repeat PAFI procedure at week 30.9	No	N/A	2	35.7	35.7	No
6	Healed	None	Yes	5	1	2.9	60.3	No
7	Healed	None	Yes	7	1	6.0	45.4	No
8	Unhealed	Drainage	No	N/A	1	–	39.4	N/A
9	Healed	None	No	N/A	1	3.0	35.7	No
10	Unhealed	Drainage	Yes	14	1	–	21.0	N/A
11	Unhealed	Drainage	Yes	7	1	–	15.1	N/A
12	Unhealed	None; repeat procedure at 17.3 weeks	Yes	7	2	21.0	23.9	No
13	Healed	None	Yes	7	1	6.0	8.6	No
14	Healed	None	Yes	7	1	6.0	20.3	Recurrence noted at week 20.3
				7.6 ± 2.5 [7.0, (7.0–7.0)]	1.1 ± 0.4 [1.0, (1.0–1.0)]	9.0 ± 12.8 [3.6, (2.9–6.0)]	37.6 ± 20.1 [35.7, (20.8–50.6)]	

Errors represent standard deviation of the mean. Median and IQR are included in [], where applicable

N/A not applicable

$n = 11$ (78%) participants had healed, with a median time to fistula closure of 3.6 (IQR 2.9–6.0) weeks (Table 3).

Discussion

The ideal procedure for treatment of PF has been elusive because the invasive closure techniques that have higher efficacy incur higher risk, and minimally invasive techniques with lower risk generally have poor success. PAFI with OFM is a minimally invasive technique that is simple to learn and perform, and in this pilot retrospective cases series resulted in a 64% ($n = 9/14$) healing rate at 8 weeks and 78% ($n = 11/14$) were healed over the study period. There was one recurrent PF (patient #14) in the healed cohort at last follow-up and there were no significant complications in any of the study patients. These findings demonstrate the potential for PAFI with OFM to offer high efficacy with low risk in definitive treatment of PFs.

The use of biologic implants in treating PFs has been described by others previously. dECM and collagen-based implants, termed "fistula plugs", were first proposed as a minimally invasive alternative to more invasive surgical procedures based on the application of these technologies across a range of soft tissue defects [7]. However, first-generation dECM fistula plugs used in this application had relatively low clinical efficacy compared to invasive surgical procedures. For example, Bondi et al. [1] compared the clinical effectiveness of a porcine small intestine submucosa fistula plug (Surgisis®, Cook Surgical, Bloomington, Indiana, USA) to a mucosal flap procedure, and reported 12-month recurrence rates of 66% and 38%, respectively. These results were consistent with a previous study comparing a dECM fistula plug and an endorectal anal flap (ERAF) procedure, with 12-month recurrence rates of 80% and 12.5%, respectively [8].

It is interesting to speculate on the unique properties of OFM that may contribute to its success in this pilot. Previous studies on OFM have characterized its anti-inflammatory components [9] and in vitro testing has demonstrated its inhibition of tissue proteases [10], key contributors to chronic tissue inflammation [5]. More recently, OFM has been shown to recruit stem cells [9], drawing parallels to the deployment of stem cells in treatment of PF diseases [4]. In addition to the OFM implant being a different source tissue to existing fistula plugs, the OFM implant used in this series was fashioned during the operation, rather than being pre-formed as a plug, and the material can be cut to size. This approach allows for a tailored implant that can be fashioned to fit the dimensions of the patient's PF, as measured in real time by the operating surgeon. While PF included in the current case series had a length of approx. 4 cm, the approach would also be applicable to shorter PF tracts, though fistula tracts smaller than 2 cm would likely be best treated with a fistulotomy procedure with little to no morbidity. An additional advantage of the method described in this series is the low potential for local tissue disruption compared to other surgical techniques. Techniques that rely upon tissue mobilization and surgical dissection generate fibrosis within the natural tissue planes. In cases of recurrence, this scarring can make subsequent repairs more challenging and may even be prohibitive. In contrast, PAFI carries minimal risk for local scarring and does not compromise or limit subsequent surgical options. As an example from this series, two patients (#5 and #12, Table 3) who failed to heal, underwent a repeat PAFI that resulted in complete healing within 4 weeks of the second procedure. This highlights the relative ease with which the PAFI technique can be deployed, and even in the event of initial failed healing subsequent application may still lead to a successful outcome. This is consistent with wounds of various etiologies which may require multiple applications of extracellular matrix material to achieve healing.

As a retrospective pilot study, there are several limitations to this study. Most importantly, the results are based on a relatively small cohort of patients that were retrospectively reviewed and the follow-up was relatively short. However, on the basis of these initial results, further prospective studies are warranted to validate the results herein. For example, a randomized controlled trial comparing OFM-based PAFI treatment to invasive surgical intervention (e.g., LIFT) or traditional fistula plugs may be considered. Another limitation of the current case series was the absence of MRI characterization of the fistula tracts prior to treatment. Future studies would include MRI evaluations of the PF to aid in diagnosis and evaluation the extent of fistula tracts. The authors are considering prospective study designs to validate and expand the results of this study such as a randomized controlled trials comparing to OFM-based PAFI treatment with standard-of-care or existing PF treatment options such as traditional fistula plugs.

Conclusion

The promising results of this retrospective pilot case series suggest that an OFM implant may be a clinically successful and minimally invasive treatment option for the treatment of PF.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10151-023-02809-y.

Acknowledgements Funding for the study was provided by Aroa Biosurgery Limited (Auckland, New Zealand).

Data availability All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Conflict of interest BAB and SGD are employees of Aroa Biosurgery Limited (Auckland, New Zealand). JHW has received honoraria from Aroa Biosurgery Limited.

Ethical statement This study was reviewed by the LifeBridge Hospital IRB and received exempt review based on applicable federal regulations 45 CFR 46.104(d)(4).

Informed consent Informed procedural consent was obtained prior to all procedures performed. The data in this publication were later compiled and reviewed retrospectively and are presened in a de-identified format.

References

1. Bondi J, Avdagic J, Karlbom U et al (2017) Randomized clinical trial comparing collagen plug and advancement flap for transsphincteric anal fistula. Br J Surg 104(9):1160–1166
2. Iorio T, Blumberg D (2015) Short-term results of treating primary and recurrent anal fistulas with a novel extracellular matrix derived from porcine urinary bladder. Am Surg 81(5):498–502
3. Nordholm-Carstensen A, Perregaard H, Hagen KB, Krarup P-M (2021) Fistula Laser Closure (FiLaC) for fistula-in-ano-yet another technique with 50% healing rates? Int J Colorectal Dis 36(9):1831–1837
4. Lightner AL, Faubion WA (2017) Mesenchymal stem cell injections for the treatment of perianal Crohn's disease: what we have accomplished and what we still need to do. J Crohns Colitis 11(10):1267–1276
5. Bohn GA, Chaffin AE (2020) Extracellular matrix graft for reconstruction over exposed structures: a pilot case series. J Wound Care 29(12):742–749
6. Chaffin AE, Dowling SG, Kosyk MS, Bosque BA (2021) Surgical reconstruction of pilonidal sinus disease with concomitant extracellular matrix graft placement: a case series. J Wound Care 30(Sup7):S28–S34
7. Ky AJ, Sylla P, Steinhagen R, Steinhagen E, Khaitov S, Ly EK (2008) Collagen fistula plug for the treatment of anal fistulas. Dis Colon Rectum 51(6):838–843
8. Ortiz H, Marzo J, Ciga MA, Oteiza F, Armendáriz P, de Miguel M (2009) Randomized clinical trial of anal fistula plug versus endorectal advancement flap for the treatment of high cryptoglandular fistula in ano. Br J Surg 96(6):608–612
9. Dempsey SG, Miller CH, Schueler J, Veale RWF, Day DJ, May BCH (2020) A novel chemotactic factor derived from the extracellular matrix protein decorin recruits mesenchymal stromal cells in vitro and in vivo. PLoS ONE 15(7):e0235784
10. Negron L, Lun S, May BCH (2012) Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. Int Wound J 11(4):392–397

Original Investigation

OPEN

Surgical Reconstruction of Stage 3 and 4 Pressure Injuries: A Literature Review and Proposed Algorithm from an Interprofessional Working Group

Samir S. Awad, MD, MPH, FACS; James D. Stern, MD, FACS; Cathy T. Milne, APRN, MSN, ANP/ACNS-BC, CWOCN-AP; Shane G. Dowling, MSPAS, PA-C, CWS; Ron Sotomayor, BA, RN, CWOCN; Elizabeth A. Ayello, PhD, ETN, RN, CWON, FAAN; Leandro J. Feo Aguirre, MD, FACS, FASCRS; Basil Z. Khalaf, MD; Lisa J. Gould, MD; Michael N. Desvigne, MD, FACS, CWS; and Abigail E. Chaffin, MD, FACS, CWSP

ABSTRACT

OBJECTIVE: Stage 3 and 4 pressure injuries (PIs) present an enormous societal burden with no clearly defined interventions for surgical reconstruction. The authors sought to assess, via literature review and a reflection/evaluation of their own clinical practice experience (where applicable), the current limitations to the surgical intervention of stage 3 or 4 PIs and propose an algorithm for surgical reconstruction.

METHODS: An interprofessional working group convened to review and assess the scientific literature and propose an algorithm for clinical practice. Data compiled from the literature and a comparison of institutional management were used to develop an algorithm for the surgical reconstruction of stage 3 and 4 PIs with adjunctive use of negative-pressure wound therapy and bioscaffolds.

RESULTS: Surgical reconstruction of PI has relatively high complication rates. The use of negative-pressure wound therapy as adjunctive therapy is beneficial and widespread, leading to reduced dressing change frequency. The evidence for the use of bioscaffolds both in standard wound care and as an adjunct to surgical reconstruction of PI is limited. The proposed algorithm aims to reduce complications typically seen with this patient cohort and improve patient outcomes from surgical intervention.

CONCLUSIONS: The working group has proposed a surgical algorithm for stage 3 and 4 PI reconstruction. The algorithm will be validated and refined through additional clinical research.

KEYWORDS: bioscaffold, negative-pressure wound therapy, ovine forestomach matrix, pressure injury, surgical reconstruction

ADV SKIN WOUND CARE 2023;36:249–58.

DOI: 10.1097/01.ASW.0000922708.95424.88

INTRODUCTION

Pressure injuries (PIs) place a substantial burden on patients and the hospital systems that manage these complex wounds. In the US, there are roughly 2.5 million PIs per year, with approximately 30% occurring in long-term care facilities.[1] In 2019, PIs cost the US healthcare system an estimated $26.8 billion with 59% of those costs being attributed to stage 3 and 4 PIs.[2] The incidence and severity of PIs are dependent on the site of care. For example, in the acute care setting, medical-surgical inpatient care units have the lowest overall PI prevalence (7.78%), whereas critical care units have the highest overall PI prevalence (14.32%).[3] Patients in the critical care setting also develop more severe PIs, proportionally higher than in step-down or medical-surgical units.[3]

In addition to the financial burden, there is a significant toll on patients' mental health and health-related quality of life.[4] Pain, discomfort, wound exudate management, odor, and loss of mobility are all factors that reduce PI patients' quality of life.[5,6] In addition, these psychosocial and physiological patient factors negatively impact wound healing.[7] The complexity and challenges of managing PIs are probably best reflected by the difficulty in assessing the true mortality attributed to PIs; there are no reports that accurately estimate the number of patients who die every year as a result of these complex soft-tissue defects.

The incidence of PIs is related to both intrinsic and extrinsic factors.[8,9] Quality improvement programs to reduce

Samir S. Awad, MD, MPH, FACS, is Professor of Surgery, Baylor College of Medicine and Chief of Surgery, Michael E. DeBakey VA Medical Center, Houston, Texas, USA. James D. Stern, MD, FACS, is Plastic Surgeon, Memorial Regional Hospital, Hollywood, Florida. Cathy T. Milne, APRN, MSN, ANP/ACNS-BC, CWOCN-AP, is Co-owner, Connecticut Clinical Nursing Associates, Bristol, Connecticut. Shane G. Dowling, MSPAS, PA-C, CWS, is Medical Science Liaison, Aroa Biosurgery Limited, Auckland, New Zealand. Ron Sotomayor, BA, RN, CWOCN, is a wound, ostomy, and continence nurse, Advent Health, Orlando, Florida. Elizabeth A. Ayello, PhD, MS, RN, ETN, CWON, FAAN, is Editor-in-Chief, *Advances in Skin & Wound Care* and President, Ayello, Harris and Associates Incorporated, Copake, New York. Leandro J. Feo Aguirre, MD, FACS, is Colorectal Surgeon, Palm Beach Health Network, Del Ray Beach, Florida. Basil Z. Khalaf, MD, is Wound Care Physician, The MEDIKAL Group, Houston, Texas. Lisa J. Gould, MD, is Plastic Surgeon, South Shore Health, Weymouth, Massachusetts. Michael N. Desvigne, MD, FACS, CWS, is Plastic Surgeon, Desvigne Plastic Surgery and Abrazo Health, Scottsdale, Arizona. Abigail E. Chaffin, MD, FACS, CWSP, is Associate Professor of Surgery and Chief, Division of Plastic Surgery, Tulane University and Medical Director, MedCentris Wound Healing Institute, New Orleans, Louisiana. **Acknowledgments:** All of the authors are members of the interprofessional working group convened by Aroa Biosurgery Limited (Auckland, New Zealand) and were compensated for their time and travel at the group's meeting. Shane G. Dowling is an employee of Aroa Biosurgery Limited. The authors have disclosed no other financial relationships related to this article. Submitted December 6, 2022; accepted in revised form February 7, 2023.

the rates of hospital-acquired PIs are now commonplace and aimed first at prevention and second at reducing the incidence of stage 3 and 4 PIs.[10] Holistic preventive protocols focus on identifying at-risk patients; using appropriate off-loading beds; and addressing incontinence, nutrition regimens, and proper skin care.[8,11] These efforts have been augmented by new technologies to reduce the risk of PI formation, including pressure detection monitors,[12] advanced support surfaces,[13] electrical stimulation,[14] thermography,[15] and subepidermal moisture scanners.[16,17] Despite these efforts, PIs continue to occur.

Much has been written about managing PIs with standard wound management. These guidelines are founded on the key tenets of modern wound care, including pressure redistribution, moisture management, and wound bed preparation.[8,18] Although managing PIs with traditional wound care can be successful, it is often a relatively slow process. In a randomized controlled trial (RCT) assessing stage 3 and 4 PIs, only 13% of wounds (10/75) healed within 1 year, with a median healing time of 117.7 days.[19] In comparison, when standard wound care is used for stage 2 PIs, the average healing time is approximately 23 days.[20]

When traditional wound care approaches have limited success due to the involvement of deeper tissues and exposed structures, surgical reconstruction has an important role to play. Surgical reconstruction as a means of PI closure is relatively common, although there is a dearth of data to describe the frequency of surgical intervention as a proportion of all PI treatments. Early reports indicated that stage 3 and 4 PIs heal faster and with less scar tissue following surgical intervention,[21] but there is a lack of contemporary controlled studies.

In their review of inpatient PI management, Bauer et al[22] identified a total of 676,435 patients with PI, of which 26% were stage 3 or 4. Approximately 50% of patients (n = 65,582) underwent an excisional (surgical) debridement, and of these, only 5,462 patients underwent multiple excisional debridements. This number suggests that the overall proportion of PIs undergoing surgical intervention is relatively low, even when the incidence and burden of PIs are high. There may be several reasons for this, including available professional resources, health economics, comorbidities, and high complication rates.

The management of complex PIs requires an interprofessional approach with support from the hospital system, patient, family, and multiple specialties. The burden of putting this team together and needing the support of the hospital may limit the number of clinical teams willing to take on these complex reconstructions. In addition to the difficulties in assembling the required team to manage PIs, the many complications seen with PI flap reconstruction can deter both clinicians and hospitals from taking on these patients.[23–25]

The burden of PIs, advances in modern adjunctive therapies (eg, negative-pressure wound therapy [NPWT] and bioscaffolds), and the challenges to surgical reconstruction of PIs led the authors to convene an interprofessional working group with the intent to review the literature to subsequently develop an algorithm aimed at reducing complications while improving closure rates associated with the surgical management of PIs. The premise of the group was to develop a structured algorithm that blended state-of-the-art techniques and technologies to create a protocol for the surgical management of PIs.

METHODS

An interprofessional working group from various sites of care convened to discuss and establish a framework for the surgical reconstruction of PIs. Participants included four plastic surgeons; two general surgeons; one colorectal surgeon; and three wound, ostomy, and continence nurses. The participants were from 10 institutions in seven US states. All participants had specialty wound care training and practiced across the continuum of care, including inpatient surgical and acute care, long-term acute care, and outpatient wound care.

Members of the working group were separately interviewed (virtually) prior to convening an in-person discussion. The interviews were conducted to document insights into the current management, challenges, and barriers to the surgical management of stage 3 and 4 PIs. Discussion topics included:

- Patient selection criteria for surgical intervention versus standard wound care
- Proportion of patient population undergoing surgical intervention
- Wound bed preparation and patient preoperative optimization prior to surgical intervention
- Goals of surgical intervention
- Reconstructive procedures (eg, muscle or fasciocutaneous advancement flap, skin graft)
- Preoperative and postoperative offloading protocols
- Use of NPWT for PI management and closure (both surgical and standard wound care)
- Current use of bioscaffolds to augment surgical debridement and reconstruction

The preliminary interview data were used to frame the discussion during an in-person meeting held in Dallas, Texas, in October 2022 that was convened with the objective of developing a clinical algorithm for the surgical management of stage 3 and 4 PIs.

LITERATURE SYNTHESIS

Prior to convening the working group, the senior author undertook a literature review using PubMed and the following search terms or combinations thereof: "pressure injury," "pressure ulcer," "surgical reconstruction," "wound

management," "NPWT," "bioscaffold," "cellular tissue product," "acellular dermal matrix," and "complications." No limits were placed on the publication year.

The literature search identified published clinical literature relating to:

- Surgical reconstruction of stage 3 and 4 PIs
- Standard wound management for stage 3 and 4 PIs
- The use of NPWT as adjunctive therapy to standard wound care and surgical reconstruction of PIs
- The use of bioscaffolds for standard wound care and surgical reconstruction of PIs

After reviewing abstracts, the senior author accessed and screened approximately 75 relevant full-text articles. Of these, the senior author determined that 31 were relevant for the group. These articles were then sent to working group members to review prior to the meeting.

Patient Factors

All members of the working group emphasized the importance of patient optimization as part of their own preoperative patient goals. One of the key patient optimization factors identified was nutrition, including high-calorie, high-protein nutrition supplements containing arginine, zinc, and antioxidants if deficiencies are present.[8,26] This recommendation was supported by evidence from high-quality RCTs concluding that when implemented for more than 4 weeks, these diets lead to increased PI healing.[27,28] As part of patient optimization, nicotine cessation counseling was recommended because smoking has previously been linked to poor healing outcomes.[29] Further, elevated hemoglobin A_{1c} levels have been linked with high rates of postoperative complication across multiple wound etiologies.[30–32]

Based on the available clinical evidence, the working group concluded:

- All patients with stage 3 or 4 PIs should be on a high-calorie, high-protein diet containing arginine, zinc, and antioxidants.
- Patients should be counseled on nicotine use cessation prior to any definitive surgical procedure.
- Patient HbA_{1c} should be controlled as part of preoperative optimization.

Surgical Intervention for Stage 3 or 4 PIs

For stage 3 or 4 PIs that do not respond to traditional wound care, providers may consider surgical intervention. Despite a variety of surgical approaches, the goal with each approach is to remove any necrotic tissue and cover the wound defect with healthy, vascularized tissue.[33] Surgical interventions for PIs begin with a sharp debridement and can progress to a variety of different closure methods. Although sharp debridement remains the standard modality, newer ultrasonic devices have found a place in the debridement of PIs.[34]

The goal of surgical intervention is primarily to provide tissue coverage (particularly in the presence of bony prominences) and tissue infill, bearing in mind that stage 3 and 4 PIs often present with significant depth, wound bed irregularity, and tunneling/undermining. Tissue transfer in the context of PI reconstruction may include primary closure;[35] skin grafting;[36] local, muscle, or musculocutaneous flaps;[37] fascial or fasciocutaneous flaps;[23,24] perforator flaps;[38] or free tissue flaps.[39]

Several surgical techniques and modifications have been described over the past decades, but limited clinical outcomes data have been published. In a 2022 Cochrane review,[40] only one RCT was identified that investigated the surgical reconstruction of PIs.[41] In this study, Gargano et al[41] enrolled 20 patients randomized to either a conventional flap or a novel cone flap; the novel cone cohort had reduced recurrences compared with the standard flap group. Based on the current clinical evidence, there are no clear recommendations on the preferred surgical management for stage 3 and 4 PIs.[42] This view was reinforced by the working group; each of the surgeons described the use of different techniques during PI reconstruction.

As it relates to the relatively high postoperative complication rates observed following reconstruction, the working group identified three contributing factors: bacterial/biofilm contamination, dead space, and local tissue inflammation. The DNA sequencing of chronic wounds, including PIs, has identified several categories of bacteria such as aerobes, facultative anaerobes, and strict anaerobes.[43] In PIs, the majority of the bacteria detected were strict anaerobes, which are associated with biofilm formation.[43] The presence of a biofilm is a hindrance to wound healing and is a major reason why debridement is necessary to promote healing in PIs.[44] On its own, debridement is an effective surgical tool, although providers may consider complementary tools such as wound cleansers (eg, hypochlorous acid)[45,46] and fluorescence-guided debridement.[47]

In conjunction with a high bacterial burden, it is common for PIs to contain elevated concentrations of wound proteases (eg, matrix metalloproteinases and neutrophil elastase) that contribute to an ongoing inflammatory state.[48] Much has been written about addressing wound proteases in the context of wound bed preparation,[49,50] targeting proteinases as a therapy for wound chronicity,[51] and interventions that modulate wound proteases.[52]

One feature of PIs is their size and depth relative to other surgical wounds, which can prove challenging during surgical reconstruction. Kim et al[53] quantified the volume of ischial PIs using MRI from eight patients and determined a mean volume of approximately 100 cm^3. The term "dead space" is often used in the literature to refer to this characteristic[54,55] and used more generally in reconstructive surgery to describe when closure results in

a subcutaneous pocket.[56–58] Dead space has the potential to fill with fluid, resulting in a seroma or hematoma and downstream sequelae (eg, infection, tissue necrosis).[53] Seroma and/or hematoma resulting from surgical dead space in PI flap reconstruction is a relatively common complication,[23] leading to increased hospital and outpatient visits and an increase in local wound complications necessitating further surgical intervention.[59] Techniques and technologies to obliterate surgical dead space are varied and include suture anchors,[60] tissue adhesives, quilting sutures, and NPWT.[61] In vivo studies have demonstrated that the addition of bioscaffold materials to surgical dead space reduces seroma formation in a dose-dependent manner.[62]

Based on the current clinical evidence, the working group concluded:

- Common to the surgical reconstruction of all chronic tissue defects, sharp (or ultrasonic) debridement is critical to the success of the surgical reconstruction of PIs.
- No single tissue-transfer procedure (eg, free or local flaps) is generally applicable to the reconstruction of all PIs.
- The selected surgical approach should be tailored to the individual PI and decided by the training of the attending surgeon.
- Although complication rates are high, these may be addressed by adjunctive therapies to address bacterial contamination, local tissue inflammation, and dead space.

NPWT as Adjunctive Therapy for Stage 3 and 4 PIs

The use of NPWT for PI management and treatment is now the criterion standard and has available clinical evidence from case reports, case series, RCTs, and prospective real-world trials. Song et al[63] included 16 RCTs in a systematic review and meta-analysis, concluding that NPWT shortened the healing time of PIs and reduced dressing change frequency and overall hospitalization costs. As it relates to the surgical reconstruction of PIs, two variations of traditional NPWT have recently emerged that are additional tools for clinicians surgically treating PIs. Negative-pressure wound therapy with periodic instillation of fluid (NPWTi-d) is designed to be used with wound cleansers such as hypochlorous acid, aids hydrolytic debridement, and promotes a moist environment. Further, NPWTi-d may be applicable to patients with PI who are not candidates for immediate surgical reconstruction; it is effective in the removal of bacterial contamination, slough, and necrotic tissues as part of PI management.[64,65]

Closed-incision NPWT (iNPWT) has been used on high-risk closed surgical incisions to reduce surgical site infections and wound complications.[66] Use of iNPWT is now widespread across many surgical reconstruction procedures and has been reported in PI reconstruction with promising results.[67,68] A 2022 Cochrane review concluded that iNPWT decreased the incidence of surgical site infections, but reductions in surgical wound dehiscence and seroma/hematoma prevention were not conclusive.[66] Based on the available clinical evidence, the working group concluded that:

- NPWT can augment the reconstruction of PIs.
- The type of NPWT should be selected based on patient needs and available resources.

Bioscaffolds in PI Reconstruction

Biomaterials are now a part of the reconstructive ladder and are common in a variety of procedures.[69] These devices scaffold the patient's own cells leading to tissue regeneration.[69] The technologies are varied, and the working group settled on the term "bioscaffold" to describe the group of technologies including placental-derived products, synthetic devices manufactured from naturally occurring polymers (eg, reconstituted collagen) and advanced extracellular matrix devices isolated from mammalian tissue sources. The working group recognized that there is an array of terms to describe this collection of products (skin substitute, cellular and/or tissue-based products, dermal matrices, etc).

Such bioscaffolds commonly augment standard wound management of PIs (Table 1).[70–84] They are typically reapplied weekly to heal via secondary intention. When used with NPWT, the inclusion of a bioscaffold as part of standard wound management improves healing outcomes relative to NPWT alone in stage 4 PIs.[85]

Although the use of these technologies to augment wound care is commonplace, evidence for the use of bioscaffolds to augment the surgical reconstruction of PIs is sparse (Table 1). For example, a 2022 review of the surgical applications of acellular dermal matrices across the spectrum of reconstructive procedures makes no mention of PI reconstruction.[69] The working group identified only three published case series describing the use of bioscaffolds in the reconstruction of stage 3 or 4 PIs (Table 1). Vallery and Shannon[86] described the single application of Restrata Wound Matrix (Acera Surgical Inc) to build granulation tissue prior to a flap reconstruction of 11 PIs. Golla and Kurtz Phelan[87] described the placement of a cryopreserved placental membrane containing viable cells prior to muscle flap closure in four patients with stage 4 PI. Finally, Desvigne et al[88] described the flap-based reconstruction of three stage 4 PIs using ovine forestomach matrix.

Although bioscaffolds have value across a range of contaminated and inflamed soft-tissue defects, the absence of published literature describing biomaterial use for PI reconstruction led the working group to conclude:

- The cost of bioscaffolds varies widely. As such, the use of certain bioscaffolds in PI reconstruction may be cost prohibitive, given the uncertainty in outcomes and the complications associated with PI reconstruction.

Table 1. ARTICLES DESCRIBING BIOSCAFFOLD USE AND SURGICAL RECONSTRUCTION IN PI MANAGEMENT

Reference	Product	Treatment Method	No. of PIs/ Total Wounds	PI Stage (n)	PI Location	Healing time
Lullove,[70] 2017	Endoform (Aroa Biosurgery)	Secondary intention	3/53	ND	Lower extremity	Mean time to close, 12 wk
Raizman et al,[71] 2020	Endoform	Secondary intention	8/33	Stages 3 (3) and 4 (5)	Lower extremity and pelvic	3/8 > 50% reduction at 4 wk
Ferreras et al,[72] 2017	Endoform	Secondary intention	8/193	ND	Lower extremity	5/8 healed; mean time to heal, 50.8 d
Liden and May,[73] 2013	Endoform	Secondary intention	1/24	ND	Lower extremity	82% healed at 12 wk
Kloeters et al,[74] 2016	Promogran (3 M)	Secondary intention	23/33 (RCT vs SoC)	ND	ND	At 12 wk, 65% PAR
Bain et al,[75] 2020	Puraply Antimicrobial (Organogenesis)	Secondary intention	45/307	ND	ND	51% healed at wk 26
Lintzeris et al,[76] 2018	Puraply Antimicrobial	Secondary intention	3/9	Stages 3 (1) and 4 (2)	Sacral	1/3 healed by wk 20
Oropallo,[77] 2019	Puraply Antimicrobial	Secondary intention	18/41	ND	Sacral and lower extremities	7/18 healed by wk 12
Herron,[78] 2021	Restrata Wound Matrix (Acera Surgical)	Secondary intention	1/1	Stage 4 (1)	Sacral	ND
Brown-Ertis et al,[79] 2019	OaSIS Wound Matrix (Cook Biotech)	Secondary intention	67/130 (RCT vs SoC)	Stages 3 (39) and 4 (28)	ND	40% healed at 12 wk
Beers et al,[80] 2016	OaSIS® Wound Matrix	Secondary intention	3/3	3 = stage 4	Pelvic	Healed by week 11
LeCheminant and Field,[81] 2012	MatriStem (ACELL), Cytal Wound Matrix (ACELL)	Secondary intention	3/34	ND	Heel	ND for PIs; all wounds mean time to healing 35 wk
Kim et al,[82] 2021	Morselized acellular dermal matrix	Secondary intention	1/1	Stage 4 (1)	Sacral	ND
Berhane et al,[83] 2019	Epifix (Wishbone Medical)	Secondary intention	10/10	Stages 2 (2) and 3 (8)	Pelvic and lower extremity	3/8 healed by wk 8
Anselmo et al,[84] 2018	Grafix Core	Secondary intention	1/3	ND	Heel	Healed at wk 4
Vallery and Shannon,[86] 2022	Restrata Wound Matrix	Wound bed preparation prior to flap closure	11/11	ND	Pelvic	100% healed after flap closure
Golla and Kurtz Phelan,[87] 2019	Grafix Core (Smith + Nephew)	Bioscaffold as implant under musculocutaneous flap	4/4	Stage 4 (4)	Pelvic	All incisions healed, mean 7 wk
Desvigne et al,[88] 2020	Myriad Matrix (Aroa Biosurgery)	Bioscaffold as implant under fasciocutaneous flap	3/9	Stage 4 (3)	Pelvic	All PIs remained healed at 6 mo

Abbreviations: ND, not defined; PAR, percentage area reduction; PI, pressure injury; RCT, randomized control trial, SoC, standard of care.

• Not all biomaterials may be suitable to the relatively demanding environment of a PI. For example, synthetic dermal matrices may not be suitable for PI reconstruction as they have relatively high rates of infection.[89,90] Reconstituted collagen bioscaffolds are known to be less effective at modulating wound proteases relative to extracellular matrix-based devices.[52]

SURGICAL ALGORITHM

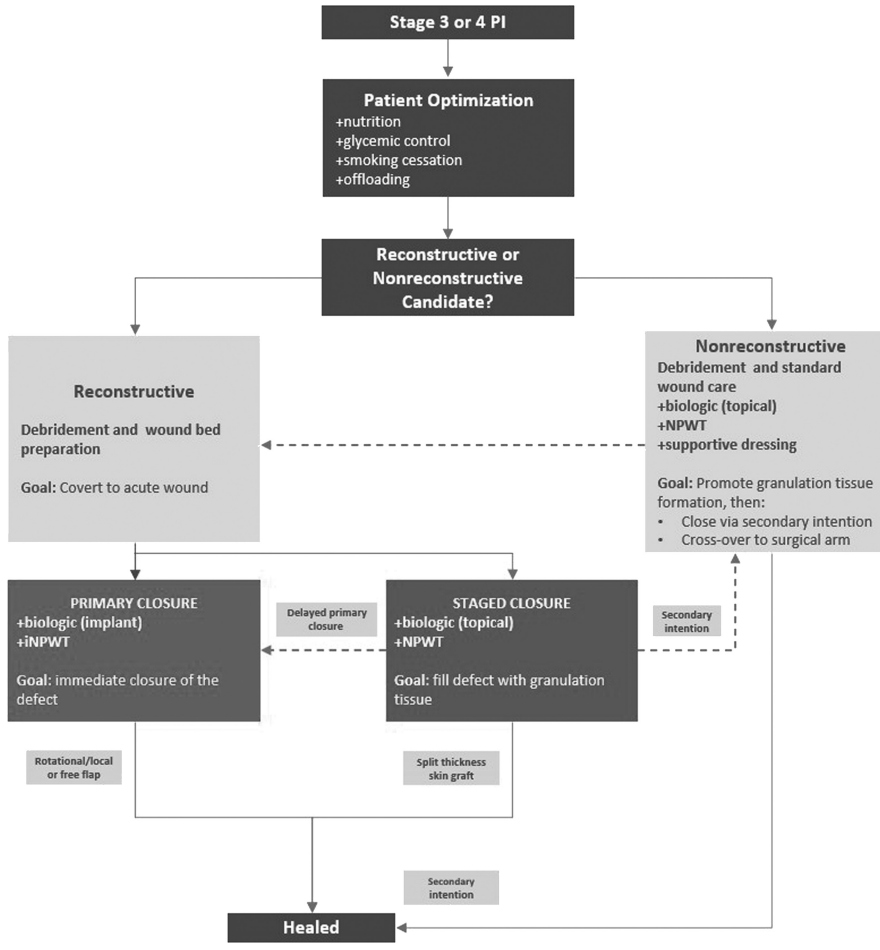
The proposed surgical algorithm developed by the working group can be found in the Figure. Rationale for the treatment pathways is provided in the following sections, building on the available clinical literature for the reconstruction of PIs.

Patient Optimization

The working group felt that all patients should be medically optimized before surgery, including:

- Nutrition status, including consultation
- Nicotine use cessation (both smoking and vaping)
- Efforts to improve glycemic control
- Osteomyelitis workup (including multiple bone biopsies)
- Improved patient pressure redistribution through proper cushion selection and needed accessories

Figure. PROPOSED SURGICAL ALGORITHM FOR THE TREATMENT OF STAGE 3 AND 4 PRESSURE INJURIES



- Appropriate local wound bed preparation[49]
- Assess and improve patients' social support systems[49]

Patient Selection

Patients can be divided into reconstructive and nonreconstructive candidates with their medical comorbidities dictating whether they could safely undergo anesthesia (Table 2). The criteria listed in Table 2 can serve as a framework for assessing whether a patient is a surgical candidate. Ultimately, clinical judgment may supersede these criteria.

Nonreconstructive candidates. For the nonreconstructive patients, PIs may be managed with standard wound care independent of the site of care (ie, inpatient vs outpatient; Figure). As part of wound bed preparation, sharp debridement should be performed if tolerated by the patient. Alternatively, autolytic debridement or enzymatic debridement may be used until the wound is free of necrotic tissue. Providers may also consider NPWTi-d. To augment standard wound care, providers should consider the addition of a bioscaffold and/or NPWT once the wound no longer has necrotic tissue with the goal to reduce the time to heal, pain, and dressing change frequency. If the wound responds, as evidenced by improvements in the granulation tissue and/or epithelial advancement, treatment should continue with a goal to close via secondary intention. If the wound bed shows improvement, and/or the patient's medical conditions improve,

Table 2. ALGORITHM RECOMMENDATIONS FOR SURGICAL RECONSTRUCTION CRITERIA OF STAGE 3 AND 4 PRESSURE INJURY

Inclusion Criteria	Exclusion Criteria
- Stage 3 or 4 pressure injury	- Under palliative care
- Adequate nutrition status	- No anesthesia clearance
- Ability to comply with postsurgical recommendations	- Poor mental status
	- No social support/resources
	- Severe malnutrition
	- Unwillingness to stop nicotine use
	- Unresectable pelvic osteomyelitis

they may be considered for "crossover" into the reconstructive intervention arm of the algorithm (Figure).

Crossover. It is not always possible to predict a patient's healing trajectory or suitability for surgery. As such, the working group discussed patients who may be originally designated as a nonreconstructive candidate but improve their medical comorbidities and/or wound bed and therefore meet surgical clearance (Figure). This reflects the complexity of PIs over the lifetime of the wound, changes in site of care, and available resources.

Reconstructive candidates. The working group concluded that, where appropriate, patients with pelvic PIs should undergo fecal diversion to reduce risk of downstream fecal contamination of the surgical site.[91] Surgical intervention should consider debridement of any necrotic bone or large bony prominences. In addition, multiple bone biopsies, harvested during debridement, should be sent to pathology to evaluate for osteomyelitis and to microbiology to identify bacterial pathogens for targeted antibiotic therapy.[92,93] Given the wide variety of available tissue-transfer procedures and patient factors (PI location, available tissue), it was concluded that the attending surgical team is best positioned to decide on the appropriate reconstructive approach. If the wound can be surgically closed after a debridement using a muscle flap, musculocutaneous flap, or fasciocutaneous flap closure, a bioscaffold may be considered for implantation at the base of the surgical site prior to closure to reduce local inflammation and obliterate dead space. An iNPWT device may aid long-term outcomes by reinforcing and protecting the surgical closure during the initial period of healing. All members of the working group felt that the inclusion of surgical drains was necessary to help with fluid removal and reduce the risk of seroma.

If the patient cannot undergo a surgical closure after a debridement, a bioscaffold may be applied to the wound bed, ideally with NPWT to augment healing. The goal in this scenario is to rapidly build well-vascularized tissue to fill the tissue defect and cover exposed structures. Once this immediate goal is achieved, then several options become available:

- Definitive closure via placement of split-thickness skin graft, depending on the location of the PI
- Closure via secondary intention using standard wound care; a bioscaffold and/or NPWT may be included to accelerate epithelialization
- Reconstructive procedures such as muscle, musculocutaneous, or fasciocutaneous flap closure

Product Selection

A wide variety of commercially available bioscaffolds are available for the management of stage 3 and 4 PIs. In the absence of high-quality clinical data, the working group chose to make general product recommendations rather than recommend specific products by name. The working group concluded:

- Given the inflammatory state of PIs and the known elevated concentrations of wound proteases, bioscaffolds that modulate wound proteases may be considered as an adjunct. This is applicable as part of standard wound care and during surgical reconstruction.
- Many PIs are colonized. Providers should consider products that are tolerant of bacterial contamination, especially to augment surgical reconstruction. In the surgical realm, avoid synthetic bioscaffolds because these are prone to infection, potentially leading to delayed healing and graft loss.
- Providers should carefully consider the affordability of the selected product. Surgical reconstruction of PIs is associated with high complication rates, often resulting in reoperation. The use of high-cost products without certainty of outcomes is not recommended.
- Match the product selected to the site of care and available resources. This is especially important in the management of PIs via standard wound care when not all products are readily available or they may incur a high cost, especially in light of weekly dressing change frequency.
- Consider morselized (ie, powdered) products to achieve tissue infill of tunneled, undermined, and irregular wound bed surfaces.
- Consider a product with sufficient volume to fill available dead space.
- If the product is to be used under a flap, then ensure the selected product is indicated for implantation (versus topical use only).
- Avoid bioscaffolds that require repeat (eg, weekly) applications to build viable tissue. Repeat OR visits reduce patient morale, increase the risk of surgical and anesthesia complications, and increase overall costs.

Based on these criteria, the working group collated applicable product and scientific information as a source for product selection (Table 3). Products selected for inclusion in Table 3 have existing published clinical evidence for use in the management or surgical reconstruction of PIs. Before applying a bioscaffold, ensure that it is covered by the healthcare system.

CONCLUSIONS AND LIMITATIONS

The purpose of the working group was to review and make recommendations for the treatment of stage 3 or 4 PIs with a focus on surgical reconstruction and closure. To the authors' knowledge, this is the first proposed surgical algorithm for stage 3 and 4 PIs that brings together available technologies, namely, NPWT and bioscaffolds, in an attempt to better patient outcomes.

This initiative was driven in part by the absence of clinical literature to describe a holistic approach to surgical intervention and is proposed as a starting point for

Table 3. PRODUCT SELECTION GUIDE

Product	Description	Wound Protease Modulation	Tolerates a Contaminated Defect	Affordability,[a] USD/cm^2	Morselized Format Available?	Thickness, mm	Indications for Implantation	Typical Usage
Endoform	Ovine forestomach ECM	Yes[52]	Yes[70–73]	$0.54	No (see Myriad Matrix)	0.25[96]	No	Weekly application
Promogran	Reconstituted bovine collagen	Yes[97,98]	ND	$0.78	No	3.0[99]	No	Weekly application
Puraply Antimicrobial	Crosslinked porcine intestine ECM and PHMB	ND	Yes[75,100]	$81.33	No	0.05[b,101]	No	Weekly application
Restrata Wound Matrix	Synthetic (PGLA/PDO)	ND	Yes[86]	$93.22	No	0.5[102]	No	Weekly application
OaSIS Wound Matrix	Porcine intestine ECM	Yes[103]	Yes[79]	$9.68	Yes	0.05 (one layer)[101]	No	Weekly application
MatriStem, Cytal Wound Matrix	Porcine bladder ECM	ND	Yes[104]	ND[b]	Yes	0.05 (one layer)[105]	No	Weekly application
Morselized acellular dermal matrix[c]	Human dermis ECM	ND	Yes[82]	ND[b]	Yes	NA	No	Weekly application
Epifix	Human placental	ND	Yes[83]	$162.46	Yes	0.07-0.18[106,107]	No	Weekly application
Grafix Core	Human placental	ND	Yes[84,87]	$106.56	Yes	0.25-0.5[108]	No	Weekly application
Myriad Matrix	Ovine forestomach ECM	Yes[52]	Yes[88,109,110]	$12.11	Yes	Up to 1.5 (2, 3, and 5 layer)	Yes	Single application

Abbreviations: ECM, extracellular matrix; PDO, polydiaxonone; PGLA, polyglactin 910; PHMB, polyhexamethylene biguanide; NA, not applicable; ND, not determined.
Note: Included products have published clinical evidence for use in PIs (Table 1).
[a]Indicative pricing per cm^2 based on all available product sizes, accessed November 25, 2022 from the US Department of Veterans Affairs, National Acquisition Center, https://www.vendorportal.ecms.va.gov/NAC/MedSurg/List.
[b]Product pricing not available.
[c]Product name not disclosed.

further clinical evidence gathering. The working group does acknowledge prior but limited work in this space. For example, Chen et al[94] previously proposed an algorithm for assessing when patients with a PI are candidates for flap closure, and Gargano et al[41] have made recommendations for different flap-based techniques. A Swedish postoperative algorithm described the management of patients that underwent flap-based surgical reconstruction.[95] It is important to note that the working group did not include a rehabilitation expert or a dietitian, and detailed discussions of these aspects are beyond the scope of this article.

In this current proposed algorithm, all stage 3 or 4 patients can be included in the treatment pathway, making it widely applicable to patients with PIs. For both nonreconstructive and reconstructive candidates, the postoperative weight redistribution protocol is crucial to their overall success. Multiple protocols exist that all place emphasis on a period of bed rest followed by gradual mobilization, but there is a lack of agreement on the exact time frame; this progression may occur between 2 and 6 weeks.

As acknowledged earlier, further clinical evidence is required to validate the proposed algorithm; therefore, data regarding experience using the algorithm are being collected. Additional clinical evidence may help to further refine recommendations made for the surgical management of these challenging soft-tissue defects. Given the limited clinical evidence and diverse approaches to the surgical management of PI, this proposed algorithm is not intended as a consensus document or a formal clinical guideline. Rather, this proposed algorithm is a starting point to develop future clinical evidence aimed at improving clinical outcomes in PI reconstruction. ●

REFERENCES

1. VanGilder C, Lachenbruch C, Algrim-Boyle C, Meyer S. The International Pressure Ulcer Prevalence survey: 2006-2015: a 10-year pressure injury prevalence and demographic trend analysis by care setting. J Wound Ostomy Continence Nurs 2017;44(1):20-8.
2. Padula WV, Delarmente BA. The national cost of hospital-acquired pressure injuries in the United States. Int Wound J 2019;16(3):634-40.
3. VanGilder CA, Cox J, Edsberg LE, Koloms K. Pressure injury prevalence in acute care hospitals with unit-specific analysis: results from the International Pressure Ulcer Prevalence (IPUP) survey database. J Wound Ostomy Continence Nurs 2021;48(6):492-503.
4. Essex HN, Clark M, Sims J, Warriner A, Cullum N. Health-related quality of life in hospital inpatients with pressure ulceration: assessment using generic health-related quality of life measures. Wound Repair Regen 2009;17(6):797-805.

5. Fox C. Living with a pressure ulcer: a descriptive study of patients' experiences. Br J Community Nurs 2002;7(6 Suppl):10, 12, 14, 16, 20, 22.
6. Gorecki C, Brown JM, Nelson EA, et al. Impact of pressure ulcers on quality of life in older patients: a systematic review. J Am Geriatr Soc. 2009;57(7):1175-83.
7. Charalambous C, Vassilopoulos A, Koulouri A, et al. The impact of stress on pressure ulcer wound healing process and on the psychophysiological environment of the individual suffering from them. Med Arch 2018;72(5):362-6.
8. Kottner J, Cuddigan J, Carville K, et al. Prevention and treatment of pressure ulcers/injuries: the protocol for the second update of the international Clinical Practice Guideline 2019. J Tissue Viability 2019;28(2):51-8.
9. Gefen A, Alves P, Ciprandi G, et al. Device-related pressure ulcers: SECURE prevention. 2nd ed. J Wound Care 2022;31(Sup3a):S1-72.
10. Padula WV, Malaviya S, Hu E, Creehan S, Delmore B, Tierce JC. The cost-effectiveness of sub-epidermal moisture scanning to assess pressure injury risk in U.S. health systems. J Patient Safety Risk Manage 2020;25(4):147-55.
11. Padula WV, Mishra MK, Makic MB, Valuck RJ. A framework of quality improvement interventions to implement evidence-based practices for pressure ulcer prevention. Adv Skin Wound Care 2014; 27(6):280-4.
12. Siddiqui A, Behrendt R, Lafluer M, Craft S. A continuous bedside pressure mapping system for prevention of pressure ulcer development in the medical ICU: a retrospective analysis. Wounds 2013;25(12):333-9.
13. McInnes E, Jammali-Blasi A, Bell-Syer SE, Dumville JC, Middleton V, Cullum N. Support surfaces for pressure ulcer prevention. Cochrane Database Syst Rev 2015(9):CD001735.
14. Kawasaki L, Mushahwar VK, Ho C, Dukelow SP, Chan LL, Chan KM. The mechanisms and evidence of efficacy of electrical stimulation for healing of pressure ulcer: a systematic review. Wound Repair Regen 2014;22(2):161-73.
15. Higashino T, Nakagami G, Kadono T, et al. Combination of thermographic and ultrasonographic assessments for early detection of deep tissue injury. Int Wound J. 2014;11(5):509-16.
16. Musa L, Ore N, Raine G, Smith G. Clinical impact of a sub-epidermal moisture scanner: what is the real-world use? J Wound Care 2021;30(3):198-208.
17. Peko Cohen L, Gefen A. Phantom testing of the sensitivity and precision of a sub-epidermal moisture scanner. Int Wound J 2019;16(4):979-88.
18. Boyko TV, Longaker MT, Yang GP. Review of the current management of pressure ulcers. Adv Wound Care (New Rochelle) 2018;7(2):57-67.
19. Zuloff-Shani A, Adunsky A, Even-Zahav A, et al. Hard to heal pressure ulcers (stage III-IV): efficacy of injected activated macrophage suspension (AMS) as compared with standard of care (SOC) treatment controlled trial. Arch Gerontol Geriatr 2010;51(3):268-72.
20. Palese A, Luisa S, Ilenia P, et al. What is the healing time of stage II pressure ulcers? Findings from a secondary analysis. Adv Skin Wound Care 2015;28(2):69-75.
21. Woolsey RM, McGarry JD. The cause, prevention, and treatment of pressure sores. Neurol Clin 1991;9(3):797-808.
22. Bauer K, Rock K, Nazzal M, Jones O, Qu W. Pressure ulcers in the United States' inpatient population from 2008 to 2012: results of a retrospective nationwide study. Ostomy Wound Manage 2016;62(11):30-8.
23. Bamba R, Madden JJ, Hoffman AN, et al. Flap reconstruction for pressure ulcers: an outcomes analysis. Plast Reconstr Surg Glob Open 2017;5(1):e1187.
24. Biglari B, Buchler A, Reitzel T, et al. A retrospective study on flap complications after pressure ulcer surgery in spinal cord-injured patients. Spinal Cord 2014;52(1):80-3.
25. Tran BNN, Chen AD, Kamali P, Singhal D, Lee BT, Fukudome EY. National perioperative outcomes of flap coverage for pressure ulcers from 2005 to 2015 using American College of Surgeons National Surgical Quality Improvement Program. Arch Plast Surg 2018;45(5):418-24.
26. Litchford MD. Putting the 2019 Nutrition Recommendations for Pressure Injury Prevention and Treatment into practice. Adv Skin Wound Care 2020;33(9):462-8.
27. Cereda E, Klersy C, Serioli M, Crespi A, D'Andrea F, OligoElement Sore Trial Study G. A nutritional formula enriched with arginine, zinc, and antioxidants for the healing of pressure ulcers: a randomized trial. Ann Intern Med 2015;162(3):167-74.
28. Banks MD, Ross LJ, Webster J, et al. Pressure ulcer healing with an intensive nutrition intervention in an acute setting: a pilot randomised controlled trial. J Wound Care 2016;25(7):384-92.
29. Lane CA, Selleck C, Chen Y, Tang Y. The impact of smoking and smoking cessation on wound healing in spinal cord-injured patients with pressure injuries: a retrospective comparison cohort study. J Wound Ostomy Continence Nurs 2016;43(5):483-7.
30. Wong JKL, Ke Y, Ong YJ, Li HH, Abdullah HR. Impact of preoperative HbA_{1c} on postoperative complications after elective major abdominal surgery: a systematic review protocol. BMJ Open 2020;10(9):e039422.
31. Tanaka T, Bradford T, Litofsky NS. Severity of preoperative HbA_{1c} and predicting postoperative complications in spine surgery. World Neurosurg 2021;155:e770-7.
32. Gustafsson UO, Thorell A, Soop M, Ljungqvist O, Nygren J. Haemoglobin A_{1c} as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery. Br J Surg 2009; 96(11):1358-64.
33. Wong JK, Amin K, Dumville JC. Reconstructive surgery for treating pressure ulcers. Cochrane Database Syst Rev 2016;12:CD012032.
34. Kataoka Y, Kunimitsu M, Nakagami G, Koudounas S, Weller CD, Sanada H. Effectiveness of ultrasonic debridement on reduction of bacteria and biofilm in patients with chronic wounds: a scoping review. Int Wound J 2021;18(2):176-86.
35. Simman R. Wound closure and the reconstructive ladder in plastic surgery. J Am Col Certif Wound Spec 2009;1(1):6-11.
36. Srivastava A, Gupta A, Taly AB, Murali T. Surgical management of pressure ulcers during inpatient neurologic rehabilitation: outcomes for patients with spinal cord disease. J Spinal Cord Med 2009; 32(2):125-31.
37. Sibar S, Findikcioglu K, Guney K, Tuncer S, Ayhan S. Effect of flap selection on the postoperative success of sacral pressure injuries: a retrospective analysis. Wounds 2021;33(10):271-6.
38. Koshima I, Moriguchi T, Soeda S, Kawata S, Ohta S, Ikeda A. The gluteal perforator-based flap for repair of sacral pressure sores. Plast Reconstr Surg 1993;91(4):678-83.
39. Lemaire V, Boulanger K, Heymans O. Free flaps for pressure sore coverage. Ann Plast Surg 2008; 60(6):631-4.
40. Norman G, Wong JK, Amin K, Dumville JC, Pramod S. Reconstructive surgery for treating pressure ulcers. Cochrane Database Syst Rev 2022;10:CD012032.
41. Gargano F, Edstrom L, Szymanski K, et al. Improving pressure ulcer reconstruction: our protocol and the COP (cone of pressure) flap. Plast Reconstr Surg Glob Open 2017;5(3):e1234.
42. Laing TA, Ekpete N, Oon S, Carroll SM. Surgical reconstruction of pressure ulcer defects: a single- or two-stage procedure? J Wound Ostomy Continence Nurs 2010;37(6):615-8.
43. Dowd SE, Sun Y, Secor PR, et al. Survey of bacterial diversity in chronic wounds using pyrosequencing, DGGE, and full ribosome shotgun sequencing. BMC Microbiol 2008;8:43.
44. Attinger C, Wolcott R. Clinically addressing biofilm in chronic wounds. Adv Wound Care (New Rochelle) 2012;1(3):127-32.
45. Moore ZE, Cowman S. Wound cleansing for pressure ulcers. Cochrane Database Syst Rev 2013(3): CD004983.
46. Armstrong DG, Bohn G, Glat P, et al. Expert recommendations for the use of hypochlorous solution: science and clinical application. Ostomy Wound Manage 2015;61(5):S2-19.
47. Sandy-Hodgetts K, Andersen CA, Al-Jalodi O, Serena L, Teimouri C, Serena TE. Uncovering the high prevalence of bacterial burden in surgical site wounds with point-of-care fluorescence imaging. Int Wound J 2022;19(6):1438-48.
48. Ladwig GP, Robson MC, Liu R, Kuhn MA, Muir DF, Schultz GS. Ratios of activated matrix metalloproteinase-9 to tissue inhibitor of matrix metalloproteinase-1 in wound fluids are inversely correlated with healing of pressure ulcers. Wound Repair Regen 2002;10(1):26-37.
49. Sibbald RG, Elliott JA, Persaud-Jaimangal R, et al. Wound Bed Preparation 2021. Adv Skin Wound Care 2021;34(4):183-95.
50. Tardaguila-Garcia A, Garcia-Morales E, Garcia-Alamino JM, Alvaro-Afonso FJ, Molines-Barroso RJ, Lazaro-Martinez JL. Metalloproteinases in chronic and acute wounds: a systematic review and meta-analysis. Wound Repair Regen 2019;27(4):415-20.
51. Fu K, Zheng X, Chen Y, et al. Role of matrix metalloproteinases in diabetic foot ulcers: potential therapeutic targets. Front Pharmacol 2022;13:1050630.
52. Negron L, Lun S, May BCH. Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. Int Wound J 2012;11(4):392-7.
53. Kim DG, Park ES, Nam SM, Cha HG, Choi CY. Volumetric evaluation of dead space in ischial pressure injuries using magnetic resonance imaging: a case series. Adv Skin Wound Care 2021; 34(12):668-73.
54. Tuncbilek G, Nasir S, Ozkan O, Kayikcioglu A, Mavili E. Partially de-epithelialised and buried V-Y advancement flap for reconstruction of sacrococcygeal and ischial defects. Scand J Plast Reconstr Surg Hand Surg 2004;38(2):94-9.
55. Jakubietz RG, Jakubietz MG, Jakubietz DF, et al. Ischial pressure sores: reconstruction using the perforator-based reverse flow musculocutaneous 180 degrees propeller flap. Microsurgery 2009; 29(8):672-5.
56. Gage MJ, Yoon RS, Gaines RJ, Dunbar RP, Egol KA, Liporace FA. Dead space management after orthopaedic trauma: tips, tricks, and pitfalls. J Orthop Trauma 2016;30(2):64-70.
57. Oliver RA, Lovric V, Yu Y, et al. Development of a novel model for the assessment of dead-space management in soft tissue. PLoS One 2015;10(8):e0136514.
58. Bura V, Visrodia P, Bhosale P, et al. MRI of surgical flaps in pelvic reconstructive surgery: a pictorial review of normal and abnormal findings. Abdom Radiol (NY) 2020;45(10):3307-20.
59. Kazzam ME, Ng P. Postoperative Seroma Management. Treasure Island, FL: StatPearls; 2022.
60. Lykoudis EG, Spyropoulou GA. The use of suture anchors in reconstruction of sacral pressure ulcers with gluteal fasciocutaneous advancement flaps. Ann Plast Surg 2007;59(1):92-4.
61. Massey LH, Pathak S, Bhargava A, Smart NJ, Daniels IR. The use of adjuncts to reduce seroma in open incisional hernia repair: a systematic review. Hernia 2018;22(2):273-83.
62. Agalar C, Sevinc AI, Aysal A, Egeli T, Aksoy OS, Kocdor MA. Porcine dermal collagen prevents seroma formation after mastectomy and axillary dissection in rats. Eur J Breast Health 2017;13(4): 200-5.

63. Song YP, Wang L, Yuan BF, et al. Negative-pressure wound therapy for III/IV pressure injuries: a meta-analysis. Wound Repair Regen 2021;29(1):20-33.
64. Arowojolu OA, Wirth GA. Sacral and ischial pressure ulcer management with negative-pressure wound therapy with instillation and dwell. Plast Reconstr Surg 2021;147(1S-1):61S-7S.
65. Kim PJ, Attinger CE, Constantine T, et al. Negative pressure wound therapy with instillation: international consensus guidelines update. Int Wound J 2020;17(1):174-86.
66. Norman G, Shi C, Goh EL, et al. Negative pressure wound therapy for surgical wounds healing by primary closure. Cochrane Database Syst Rev 2022;4:CD009261.
67. Hsu KF, Kao LT, Chu PY, et al. Simple and efficient pressure ulcer reconstruction via primary closure combined with closed-incision negative pressure wound therapy (CiNPWT)—experience of a single surgeon. J Pers Med 2022;12(2).
68. Papp AA. Incisional negative pressure therapy reduces complications and costs in pressure ulcer reconstruction. Int Wound J 2019;16(2):394-400.
69. Petrie K, Cox CT, Becker BC, MacKay BJ. Clinical applications of acellular dermal matrices: a review. Scars Burn Heal 2022;8:20595131211038313.
70. Lullove EJ. 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. Wounds 2017;29(4):107-14.
71. Raizman R, Hill R, Woo K. Prospective multicenter evaluation of an advanced extracellular matrix for wound management. Adv Skin Wound Care 2020;33(8):437-44.
72. Ferreras DT, Craig S, Malcomb R. 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. Surg Technol Int 2017;30:61-9.
73. Liden BA, May BC. Clinical outcomes following the use of ovine forestomach matrix (Endoform dermal template) to treat chronic wounds. Adv Skin Wound Care 2013;26(4):164-7.
74. Kloeters O, Unglaub F, de Laat E, van Abeelen M, Ulrich D. Prospective and randomised evaluation of the protease-modulating effect of oxidised regenerated cellulose/collagen matrix treatment in pressure sore ulcers. Int Wound J 2016;13(6):1231-6.
75. Bain MA, Koullias GJ, Morse K, Wendling S, Sabolinski ML. Type I collagen matrix plus polyhexamethylene biguanide antimicrobial for the treatment of cutaneous wounds. J Comp Eff Res 2020;9(10):691-703.
76. Lintzeris D, Vernon K, Percise H, et al. Effect of a new purified collagen matrix with polyhexamethylene biguanide on recalcitrant wounds of various etiologies: a case series. Wounds 2018;30(3):72-8.
77. Oropallo AR. Use of native type I collagen matrix plus polyhexamethylene biguanide for chronic wound treatment. Plast Reconstr Surg Glob Open 2019;7(1):e2047.
78. Herron K. Treatment of a complex pressure ulcer using a synthetic hybrid-scale fiber matrix. Cureus 2021;13(4):e14515.
79. Brown-Etris M, Milne CT, Hodde JP. An extracellular matrix graft (Oasis(R)) wound matrix) for treating full-thickness pressure ulcers: a randomized clinical trial. J Tissue Viability 2019; 28(1):21-6.
80. Beers PJ, Adgerson CN, Millan SB. Porcine tri-layer wound matrix for the treatment of stage IV pressure ulcers. JAAD Case Rep 2016;2(2):122-4.
81. LeCheminant J, Field C. Porcine urinary bladder matrix: a retrospective study and establishment of protocol. J Wound Care 2012;21(10):476, 478-480, 482.
82. Kim M, Jeon S, Kim SW. Successful treatment of a large coccygeal pressure ulcer using injectable acellular dermal matrix: a case report. J Wound Manag Res 2021;17(3):218-21.
83. Berhane CC, Brantley K, Williams S, Sutton E, Kappy C. An evaluation of dehydrated human amnion/chorion membrane allografts for pressure ulcer treatment: a case series. J Wound Care 2019;28(Sup5):S4-10.
84. Anselmo DS, McGuire JB, Love E, Vlahovic T. Application of viable cryopreserved human placental membrane grafts in the treatment of wounds of diverse etiologies: a case series. Wounds 2018; 30(3):57-61.
85. Mari W, Younes S, Naqvi J, et al. Use of a natural porcine extracellular matrix with negative pressure wound therapy hastens the healing rate in stage 4 pressure ulcers. Wounds 2019;31(5): 117-22.
86. Vallery M, Shannon T. Augmented flap reconstruction of complex pressure ulcers using synthetic hybrid-scale fiber matrix. Wounds 2022;33(1):1-10.
87. Golla D, Kurtz Phelan DH. Stage IV perineal pressure ulcers in immobile patients treated with surgical flap closure augmented with cryopreserved placental membrane containing viable cells. Wounds 2019;31(1):15-8.
88. Desvigne MN, Bauer K, Holifield K, Day K, Gilmore D, Wardman AL. Case report: surgical closure of chronic soft tissue defects using extracellular matrix graft augmented tissue flaps. Frontiers Surg 2020;7(173).
89. Solanki NS, York B, Gao Y, Baker P, Wong She RB. A consecutive case series of defects reconstructed using NovoSorb® Biodegradable Temporising Matrix: initial experience and early results. J Plast Reconstr Aesthet Surg 2020;73(10):1845-53.
90. Rodriguez Collazo ER, Rathbone CR, Barnes BR. A retrospective look at integrating a novel regenerative medicine approach in plastic limb reconstruction. Plast Reconstr Surg Glob Open 2017; 5(1):e1214.
91. Pussin AM, Lichtenthaler LC, Aach M, Schildhauer TA, Brechmann T. Fecal diversion does not support healing of anus-near pressure ulcers in patients with spinal cord injury—results of a retrospective cohort study. Spinal Cord 2022;60(6):477-83.
92. Brunel AS, Lamy B, Cyteval C, et al. Diagnosing pelvic osteomyelitis beneath pressure ulcers in spinal cord injured patients: a prospective study. Clin Microbiol Infect 2016;22(3):e261-8.
93. Bodavula P, Liang SY, Wu J, VanTassell P, Marschall J. Pressure ulcer-related pelvic osteomyelitis: a neglected disease? Open Forum Infect Dis 2015;2(3):ofv112.
94. Chen CY, Chiang IH, Ou KL, et al. Surgical treatment and strategy in patients with pressure sores: a single-surgeon experience. Medicine 2020;99(44):e23022.
95. Ljung AC, Stenius MC, Bjelak S, Lagergren JF. Surgery for pressure ulcers in spinal cord-injured patients following a structured treatment programme: a 10-year follow-up. Int Wound J 2017; 14(2):355-9.
96. Floden EW, Malak SF, Basil-Jones MM, et al. Biophysical characterization of ovine forestomach extracellular matrix biomaterials. J Biomed Mater Res B Appl Biomater 2011;96(1):67-75.
97. Cullen B, Watt PW, Lundqvist C, et al. The role of oxidised regenerated cellulose/collagen in chronic wound repair and its potential mechanism of action. Int J Biochem Cell Biol 2002;34(12):1544-56.
98. Nisi G, Brandi C, Grimaldi L, Calabro M, D'Aniello C. Use of a protease-modulating matrix in the treatment of pressure sores. Chir Ital 2005;57(4):465-8.
99. Karr JC, Taddei AR, Picchietti S, Gambellini G, Fausto AM, Giorgi F. A morphological and biochemical analysis comparative study of the collagen products Biopad, Promogram, Puracol, and Colactive. Adv Skin Wound Care 2011;24(5):208-16.
100. Davis SC, Gil J, Solis M, et al. Antimicrobial effectiveness of wound matrices containing native extracellular matrix with polyhexamethylene biguanide. Int Wound J 2022;19(1):86-99.
101. Shi L, Ronfard V. Biochemical and biomechanical characterization of porcine small intestinal submucosa (SIS): a mini review. Int J Burns Trauma 2013;3(4):173-9.
102. MacEwan MR, MacEwan S, Kovacs TR, Batts J. What makes the optimal wound healing material? A review of current science and introduction of a synthetic nanofabricated wound care scaffold. Cureus 2017;9(10):e1736.
103. Shi L, Ramsay S, Ermis R, Carson D. In vitro and in vivo studies on matrix metalloproteinases interacting with small intestine submucosa wound matrix. Int Wound J 2011;9(1):44-53.
104. Mundra LS, Tucker NJ, Parry JA. Urinary bladder matrix grafting versus flap coverage for acute or infected wound defects in patients with orthopaedic trauma. J Orthop Trauma 2022; 36(10):e374-9.
105. Freytes DO, Tullius RS, Valentin JE, Stewart-Akers AM, Badylak SF. Hydrated versus lyophilized forms of porcine extracellular matrix derived from the urinary bladder. J Biomed Mater Res A 2008; 87(4):862-72.
106. Mohan R, Bajaj A, Gundappa M. Human amnion membrane: potential applications in oral and periodontal field. J Int Soc Prev Community Dent 2017;7(1):15-21.
107. Koob TJ, Lim JJ, Massee M, Zabek N, Denoziere G. Properties of dehydrated human amnion/chorion composite grafts: implications for wound repair and soft tissue regeneration. J Biomed Mater Res B Appl Biomater 2014;102(6):1353-62.
108. Tan EK, Cooke M, Mandrycky C, et al. Structural and biological comparison of cryopreserved and fresh amniotic membrane tissues. J Biomater Tissue Eng 2014;4:379-88.
109. Chaffin AE, Buckley MC. Extracellular matrix graft for the surgical management of Hurley stage III hidradenitis suppurativa: a pilot case series. J Wound Care 2020;29(11):624-30.
110. Chaffin AE, Dowling SG, Kosyk MS, Bosque BA. Surgical reconstruction of pilonidal sinus disease with concomitant extracellular matrix graft placement: a case series. J Wound Care 2021; 30(Sup7):S28-34.

ePlasty

ORIGINAL RESEARCH

Ovine Forestomach Matrix in the Surgical Management of Complex Volumetric Soft Tissue Defects: A Retrospective Pilot Case Series

Michael T Cormican, MD[1]; Nathan J Creel, MD[1]; Brandon A Bosque, DPM[2]; Shane G Dowling, MSPAS[2;] Phillip P Rideout, MD[3]; William M Vassy, MD[1]

Keywords
Extracellular Matrix
Ovine Forestomach Matrix
Soft Tissue Trauma
Exposed Vital Structures
Volumetric Tissue Loss

September 2023
ISSN 1937-5719

Index ePlasty 2023;23:e66

Abstract

Background. Volumetric soft tissue loss is an urgent surgical issue and can frequently lead to suboptimal outcomes for patients due to significant soft tissue loss, compromised vital structures, and contamination. Ovine forestomach matrix (OFM) has demonstrated clinical success in the surgical management of soft tissue defects, especially in contaminated fields, and provides an effective option for immediate coverage of exposed vital structures before definitive closure.

Methods. This retrospective pilot case series (n = 13 defects) evaluated the clinical effectiveness of OFM (graft and/or particulate formats) in the surgical management of contaminated volumetric soft tissue defects. Patients presented with significant soft tissue loss, often with exposed viscera, tendon, bone, or muscle, and were treated with OFM as part of their inpatient surgical management. All patients had at least 1 significant comorbidity with the potential to complicate their healing trajectory. The primary study endpoint was time to 100% granulation tissue coverage (days), and the secondary endpoint was any device-related postoperative complications.

Results. A total of 13 volumetric soft tissue defects were evaluated in 10 patients who underwent surgical reconstruction. Mean defect age was 3.5 ± 5.6 weeks, and mean area was 217.3 ± 77.9 cm^2. Most defects had exposed structures (85%), and all defects were Centers for Disease Control and Prevention grade 2 or higher. Mean time to 100% granulation tissue formation was 23.4 ± 9.2 days, with a median product application of 1.0. Staged reconstruction was used in 7 of 13 defects, with the remainder (6 of 13) left to heal via secondary intention using standard wound care protocols. There were no major postoperative infections or adverse events (mean follow-up, 7.4 ± 2.4 weeks.)

Conclusions. This retrospective pilot case series builds on a growing body of evidence that OFM can be utilized to facilitate the formation of functional, well-vascularized soft tissue in large contaminated volumetric soft tissue defects.

Introduction

Complex soft tissue defects requiring reconstruction can be the result of a wide variety of etiologies, including necrotizing soft tissue infections (NSTIs), surgical dehiscence, burns, trauma, pressure injuries, and other etiologies. The resulting defect may heal by secondary intention but with relatively lengthy healing times involving frequent dressing changes, all while being prone to infection.[1] Surgical management of these full-thickness defects can vary widely and may include immediate coverage with a split-thickness skin graft (STSG), use of local or autologous free flaps, use of dermal matrices, and/or negative pressure wound therapy (NPWT). The current definition of a full-thickness wound is a defect that extends through the dermis, often with exposed structures (eg, bone, tendon, fascia, or muscle).[2] Often in trauma and acute care, full-thickness defects are relatively deep with loss of the dermal layer as well as the deeper subcutaneous tissue layers (eg, adipose, fascia, or muscle). To better classify the severity and depth of these defects, we propose an additional definition for these large 3-dimensional complex wounds, referring to these wounds collectively as “volumetric soft tissue defects.” This proposed terminology draws from the field of civilian and combat-related trauma where the term “volumetric muscle loss” (VML) is used to define significant loss of the musculature.[3] We propose that this terminology allows for a better visualization of the challenge in successfully reconstructing these large-volume, full-thickness dermal defects.

Initially, the primary goal of the reconstruction of a full-thickness wound is immediate coverage of exposed vital structures, such as viscera, bone, tendon, or fascia. This may be achieved via placement of a STSG, which decreases the potential for infection,[4] facilitates closure when healing by primary or secondary intention is not feasible,[5] and provides immediate coverage of any exposed structures.[6] However, in doing so, patients can be left with irregular scars that have significant differences in contour between the uninjured skin and the healed defect. In cosmetic surgery, this contour defect is often referred to as a “step-off” deformity.[7] This is exacerbated in volumetric soft tissue defects due to their depth, such that immediate application of a STSG in this scenario may lead to a step-off deformity. An alternate reconstructive approach to full-thickness and volumetric defects is a free flap procedure. However, a free flap procedure may result in overly prominent tissue requiring subsequent debulking procedures.[8] Additionally, volumetric soft tissue defects are not always candidates for local or free tissue flaps as they tend to have undermining sinus tracts and/or an irregular wound surface that can compromise the arterial blood flow necessary to facilitate flap success.[9]

Modern dermal matrices are now very much part of the reconstructive ladder and may provide an alternative to, or augment, more complex tissue transfer procedures. In some instances, dermal matrices may be deployed in the first instance so that more complex procedures can be held as a back-up to these local less invasive matrix-based approaches.[10] Dermal matrices include a variety of technologies, both synthetically manufactured or biologic, being derived from mammalian tissue extracellular matrix (ECM). ECM-based products are a good option in contaminated fields since typically synthetic dermal matrices are contraindicated for this environment as they may serve as a nidus for bacterial growth.[11] In contrast, ECM-based dermal matrices are generally tolerant of a contaminated surgical site.[12] For example, Ousey et al[13] have proposed that dermal matrices may be deployed in Centers for Disease Control and Prevention (CDC) grade 2 and grade 3 defects following adequate sharp debridement. As it relates to volumetric soft tissue defects, dermal matrices provide a robust option to traditional tissue transfer procedures (ie, STSG and free or rotational flaps) as they enable a staged approach to reconstruction, providing immediate coverage of exposed structures and tissue infill to enable contour restoration of these deep and typically irregular defects.

Ovine forestomach matrix (OFM) is a decellularized ECM biomaterial that has been fabricated into a variety of devices and utilized for soft tissue regeneration in a range of contaminated defects, including hidradenitis suppurativa,[14] pilonidal sinus,[15] chronic diabetic foot ulcers,[16] chest wall reconstruction,[17] and abdominal wall repair.[18-24] The success of OFM in these

reconstructions that involve contaminated fields can be attributed to its ability to form well-vascularized tissue[25] while modulating wound proteases that are known to prolong inflammation.[26] This, in theory, should allow the patient's immune system to primarily fend off persistent microbial contamination and progress the wound to an accelerated closure.[27]

In this retrospective pilot case series, we report our initial experience using OFM-based devices in conjunction with NPWT to provide coverage and tissue infill in volumetric soft tissue defects.

Materials and Methods

General

The retrospective study included patients who had undergone surgical reconstruction during the period January 2021 to February 2023 at a single facility. All patients provided written informed consent for their images and data to be used for research and publication purposes. The retrospective study was reviewed, and ethical oversight waived by WCG Clinical institutional review board (Puyallup, WA). The study was conducted in accordance with World Medical Association Declaration of Helsinki ethical guidelines. Patient demographics (eg, age, gender, significant baseline comorbidities), defect etiology and characteristics (eg, size, CDC grade), and outcomes (eg, 100% granulation tissue formation, recurrence, complications) were captured in Excel (Microsoft Corporation). The primary study outcome was defined as time (days) for complete graft integration and volumetric fill of the soft tissue defect with granulation tissue. Secondary endpoints included postoperative complications (eg, infection, pain, and recurrence). Descriptive statistics (eg, median, mean, SD) were computed using Excel.

Surgical Reconstruction

OFMs in either graft (Myriad Matrix Soft Tissue Bioscaffold; Aroa Biosurgery Limited) or morselized (particulate or powder) format (Myriad Morcells; Aroa Biosurgery Limited) were used according to the instructions for use. Patients were given general anesthesia, the surgical site was prepared with povidone-iodine (Betadine; Cumulus Pharmaceutical LLC), and the patient was surgically draped. The defects were thoroughly debrided to remove all necrotic tissue and lavaged with sterile saline. Defect dimensions and depth were recorded with a surgical ruler post debridement. Utilization of either the OFM graft (3- or 5-layer), morselized OFM, or a combination of the 2 products was based on clinical judgment of the attending surgeon. The OFM devices were rehydrated (<5 min, sterile saline), trimmed to size as required, and fixed to the defect edges with either suture or staples. The grafts were dressed with a nonadherent layer (Xeroform; McKesson Medical-Surgical), then NPWT interface black foam and the NPWT system (V.A.C. Therapy; 3M/KCI). NPWT systems were set to 125 mm Hg, and dressings were changed every 5 to 7 days. At dressing change, the defects were assessed for integration of the OFM graft and any complications. Complete graft integration and percentage granulation tissue formation was judged by the surgical team at the time of dressing change. At the discretion of the surgical team, definitive closure of the defects was achieved via STSG or secondary intention, according to institutional protocols.

TABLE 1. PARTICIPANT DEMOGRAPHICS

Participant#/ Defect#	Age/ Gender	Comorbidities	Defect description	Exposed structure	Wound age (weeks)	Prior surgical interventions	CDC grade	Surface area (cm^2)	Depth (cm)
1	28/M	PE/DVT, obesity, mental health disorder	High-velocity trauma; prior attempted closure resulting in abdominal dehiscence and frozen abdomen	NA	3	Surgical debridement's and attempted surgical closures (×3)	3	110.0	4.0
2A	61/F	Morbid obesity, HTN	MVA resulting in left arm trauma (Morel-Lavallee)	Tendon	1	Debridement	2	190.0	3.0
2B			MVA resulting in left leg trauma (Morel-Lavallee)	Bone	1	Debridement, failed STSG	2	140.0	1.0
3	53/F	Obesity, HTN	Prior ventral hernia repair leading to abdominal dehiscence	Exposed mesh	1	Post-dehiscence debridement	2	360.0	4.0
4	64/F	Morbid obesity, paraplegia, HTN, leukemia, DM2	Prior ventral hernia with synthetic mesh reinforcement; abdominal dehiscence with exposed synthetic mesh	Exposed mesh	1	Post-dehiscence debridement	2	304.0	3.0
5	37/M	Morbid obesity, spina bifida	Right groin NSTI (Fournier's Gangrene)	Exposed muscle, tendon	2	Debridement, antibiotics	3	300.0	3.0
6	56/T	HTN, HIV, homeless	Posterior left thigh NSTI (Fournier's Gangrene)	Tendon	1	Debridement, washout	3	210.0	2.0
7	72/F	ESRD, COPD, DM2, obesity, smoker	Traumatic injury resulting in compartment syndrome, left lower leg	NA	1	Fasciotomy	2	288.0	0.3
8A	58/M	Obesity, DM2, Afib	Right heel pressure injury (stage 4)	Bone	1	Debridement, antibiotics	3	88.0	0.5
8B			Left heel pressure injury (stage 4)	Bone	1	Debridement, antibiotics	3	135.0	0.5
9A	61/F	CHF, DM2, obesity, HTN, HLD, lupus, PE, hypothyroid, OSA	Subacute trauma, right lateral leg	Muscle	16	Debridement, antibiotics, outpatient wound care	2	190.0	0.5
9B			Subacute trauma, right posterior leg	Muscle	16	Debridement, antibiotics, outpatient wound care	2	210.0	1.0
10	36/M		Subacute trauma, right hip	Muscle	1	Debridement, antibiotics, outpatient wound care	2	234.0	20.0
	52.6 ± 14.2 (57.0)[a]				3.5 ± 5.6 (1.0)[a]			217.3 ± 77.9 (210.0)[a]	3.2 ± 5.2 (2.0)[a]

[a]Mean ± standard deviation; median is included in parentheses. Afib, atrial fibrillation; CDC, Centers for Disease Control and Prevention; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM2, diabetes mellitus type 2; DVT, deep vein thrombosis; ESRD, end-stage renal disease; F, female; HLD, hyperlipidemia; HTN, hypertension; M, male; OSA, osteoarthritis; PE, pulmonary embolism; T, transgender.

Results

Ten consecutive participants were included in the study who had presented with a total of 13 soft tissue defects at a single facility and had undergone surgical reconstruction with an OFM graft (**Table 1**). Mean participant age was 52.6 ± 14.2 years; 5 were female, 4 were male, and 1 was transgender (male-to-female). All participants except one presented with significant complicating comorbidities (**Table 1**). Surgical wound dehiscence (SWD) (23%) and trauma (38%) were the primary causes of the volumetric defects; 2 others were pressure injuries, and 1 arose from a surgical intervention (compartment syndrome). Overall mean defect age was 3.5 ± 5.6 weeks. Exposed structures (eg, bone, viscera) were present in 86% of the defects, and all defects were either CDC grades 2 (62%) or 3 (38%). The mean defect area was 217.3 ± 77.9 cm^2 with a mean depth of 3.2±5.2 cm.

TABLE 2. OUTCOMES

Participant#/ Defect#	Morselized[a]	Graft[b]	Number of product applications	Time to 100% granulation tissue (days)	%STSG take at 1 week	Over time to heal (weeks)	Complications	NPWT duration (weeks)	Last long-term follow-up visit (weeks)
1	Yes		1	21	NA	6	Minor wound dehiscence	3	6
2A	Yes	Yes	1	21	100%	4	None	3	7
2B		Yes	1	13	NA	6	None	3	
3	Yes	Yes	1	21	100%	LTFU	None	4	4
4	Yes		1	8	NA	LTFU	None	4	4
5	Yes	Yes	1	43	NA	LTFU	None	4	8
6	Yes	Yes	1	28	100%	6	None	4	8
7	Yes	Yes	1	28	NA	LTFU	None	3	5
8A	Yes		2	32	80%	7	None	4	8
8B	Yes		2	32	75%	8	None	4	
9A		Yes	1	21	100%	4	None	3	5
9B		Yes	1	21	100%	4	None	3	
10	Yes	Yes	1	15	NA	13	None	8	13
			1.2 ± 0.4 (1.0)[c]	23.4 ± 9.2 (21.0)[c]	93.6 ± 11.1% (100%)[c]	6.4 ± 2.8 (6.0)[c]		3.8 ± 1.3 (4.0)[c]	7.4 ± 2.4 (8.0)[c]

[a]Myriad Morcells.
[b]Myriad matrix.
[c]Mean ± standard deviation; median is included in parentheses. LTFU, lost to follow-up before defect closure; NA, not available; NPWT, negative pressure wound therapy; STSG, split-thickness skin graft.

Three defects were managed with the OFM matrix graft only, 4 received the OFM as a morselized format, and 6 defects received both, whereby the morselized graft was first applied to the wound bed, then the matrix graft was applied (**Table 2**). Both formats of the OFM graft were easy to deploy as part of the surgical procedure and could be trimmed to size and secured with sutures or staples as needed. The median product application was 1.0 across all defects. All defects received NPWT in conjunction with the OFM graft, with a mean duration of NPWT usage of 3.8 ± 1.3 weeks (**Table 2**). In all cases, the OFM grafts integrated into the regenerating tissue, with a mean time to complete integration of the graft and 100% granulation tissue of 23.4 ± 9.2 days.

Seven defects (54%) had a staged reconstruction in which STSG was used for definitive closure. Of those participants who received a STSG, the median STSG take at 1 week was 100%. Five of the 10 participants were lost to follow-up before complete healing, and the mean time to closure of defects in the remaining patients was 6.4 ± 2.8 weeks. There was one minor wound dehiscence reported (participant #1), but otherwise there were no infections, seromas, or other complications during the postoperative follow-up period (mean, 7.4 ± 2.4 weeks)(**Table 2**).

The following sections highlight 3 sample cases from the study data and do not reflect the chronological order of cases.

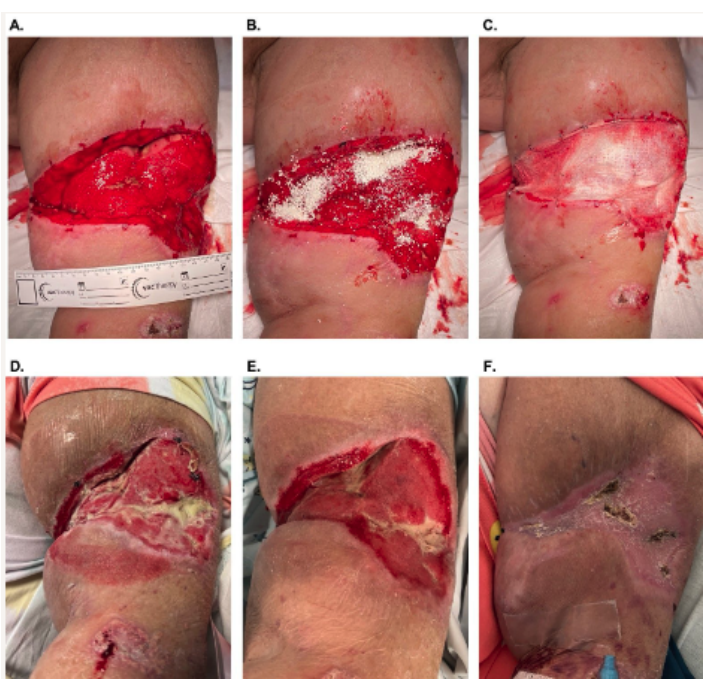


Figure 1. Case 1, participant 2, defect 2A. Traumatic defect to left arm resulting from motor vehicle accident. (A) Defect following surgical debridement. (B) Application of morselized OFM. (C) OFM graft, secured to defect perimeter. Postoperative day 13 (D), day 16 (E), and day 47, 3 weeks after application of a STSG (F). OFM, ovine forestomach matrix; STSG, split-thickness skin graft.

Case 1

A 61-year-old female patient (participant 2 ; **Table 1**) with morbid obesity and hypertension presented for follow-up evaluation of multiple soft tissue traumas sustained in a high-velocity motor vehicle accident, including Morel-Lavallee lesions of the left arm (**Figure 1**) and left leg (not shown). The patient had undergone multiple debridement procedures to both defects, and closure of the leg defect was attempted via placement of STSG that ultimately failed.

The patient was scheduled to undergo simultaneous reconstruction of the arm and leg defects with OFM. Before application of the OFM, the defects were irrigated with chlorhexidine solution, 50/50 povidone-iodine, and saline. After debridement, the arm defect measured 19 cm × 10 cm × 4 cm (**Figure 1A**). Morselized OFM was applied dry and rehydrated in situ with sterile saline and blood (**Figure 1B**). An OFM graft (10 cm × 20 cm, 5-layer) was rehydrated with saline, trimmed to size, then placed on top of the morselized OFM and secured to the defect (**Figure 1C**). The defects were dressed with an occlusive petrolatum dressing (Xeroform; Curad Medical), and a standard NPWT was placed at 125 mm Hg. NPWT was used for 3 weeks, with weekly dressing changes. Complete integration of the OFM graft and 100% granulation tissue over the exposed tendon was achieved in 21 days with the regenerated tissue being flush to the level of adjacent skin (**Figure 1E**). Definitive closure was achieved via application of a STSG at day 20, with 100% take of STSG after 1 week. At postoperative day 42, there was functional soft tissue with no complications (**Figure 1F**).

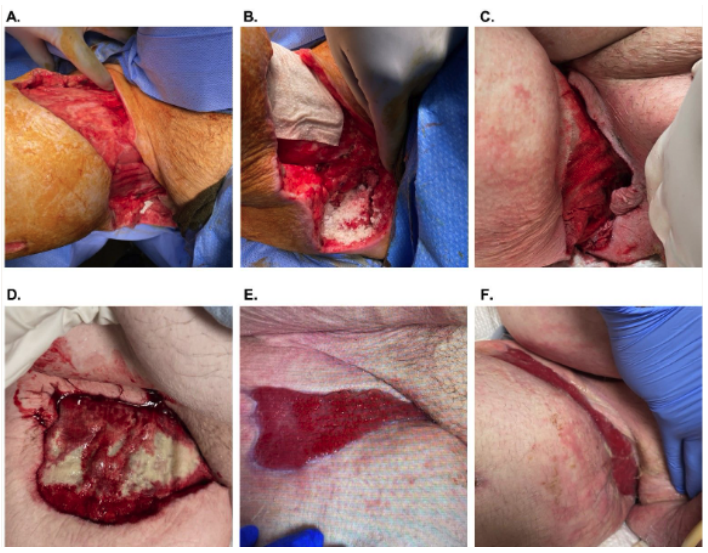


Figure 2. Case 2, participant 5. Fournier's gangrene, upper thigh and groin. (A) Defect following surgical debridement. (B) Application of morselized OFM (lower) and OFM graft (upper). Postoperative day 7 (C), day 14 (D), day 42 (E), and day 48 (F). OFM, ovine forestomach matrix.

Case 2

A 37-year-old male patient (participant 5) with obesity and spina bifida presented with an NSTI (Fornier's gangrene) of the right groin with exposed tendon and muscle (**Figure 2**). The patient had been admitted to the hospital the previous week and undergone multiple debridements and had subsequently been discharged to long-term acute care facility with standard NPWT (125 mm Hg). As the condition of the soft tissue defect continued to deteriorate, the patient was readmitted to the hospital for surgical intervention.

Upon readmission, the patient underwent surgical debridement and irrigation (chlorhexidine solution, 50/50 povidone-iodine, and saline) of the defect. After debridement, the defect measured 30 cm × 10 cm × 3 cm (**Figure 2A**). Morselized OFM was applied dry to the deepest and most irregular parts of the defect and rehydrated in situ with saline (**Figure 2B**). Two OFM grafts (10 cm × 20 cm, 5-layer) were rehydrated (saline), quilted together with absorbable polyglycolic acid suture to create a single larger graft, and then trimmed to the size of the defect. The OFM graft was applied over the morselized OFM and secured in the defect with staples (**Figure 2C**). The defect was dressed with a nonadherent layer and NPWT (125 mm Hg) as previously described. NPWT was continued for 4 weeks with weekly NPWT changes. At postoperative day 43 (**Figure 2E**), there was complete tissue coverage over the exposed bone and tendon and contour restoration. Standard wound care was initiated to close via secondary intention, and the participant was lost to follow-up after week 8.

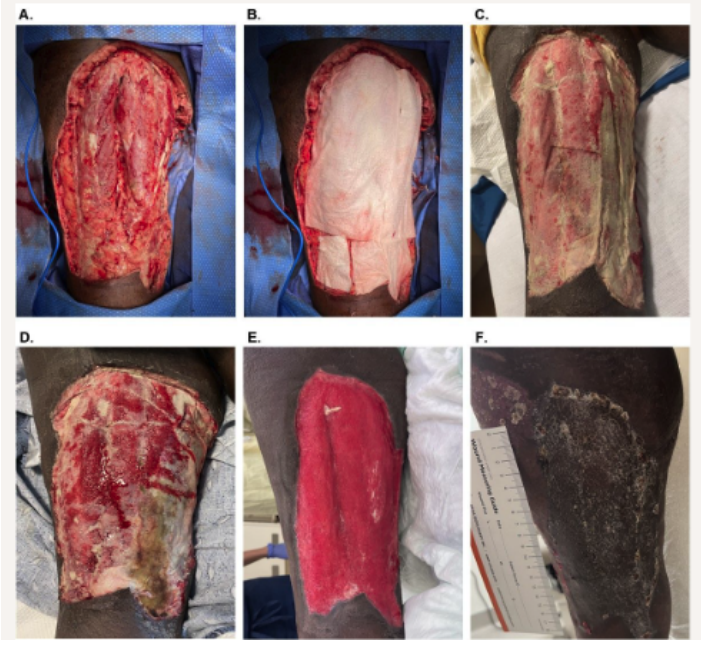


Figure 3. Case 3, participant 6. NSTI of the thigh. (A) Defect following surgical debridement. (B) Application of OFM graft. Postoperative day 12 (C), day 16 (D), day 28 (E), and day 56, 4 weeks after application of a STSG (F). NSTI, necrotizing soft tissue infection; OFM, ovine forestomach matrix; STSG, split-thickness skin graft.

Case 3

A 56-year-old transgender (male-to-female) patient (participant 6) with medical history significant for HIV infection and hypertension was experiencing homelessness and developed an NSTI of the posterior left thigh. The participant presented to the emergency department with worsening pain and swelling and was immediately admitted for surgical debridement of necrotic and infectious tissue. The patient was managed acutely by another health care professional, undergoing multiple surgical debridements over the course of several days before leaving against medical advice.

Subsequently, the patient presented to the authors' facility approximately 2 weeks after the initial admission. The patient was taken to surgery and underwent a sharp debridement, resulting in a defect measuring 21 cm × 10 cm × 2 cm (**Figure 3A**). Two OFM grafts (10 cm × 20 cm, 5-layer) were rehydrated (saline), trimmed, placed into the defect, and secured with absorbable sutures (**Figure 3B**). The graft was dressed with an occlusive petrolatum dressing (Xeroform; Curad Medical) and standard NPWT (125 mm Hg). The patient underwent dressing changes every 5 to 7 days whereby the NPWT interface foam was replaced, but the occlusive dressing was left in place so as to not disturb the underlying graft. At postoperative day 16, the graft was well adhered and had approximately 70% graft integration (**Figure 3D**). There was no sign of infection or complication, and NPWT was continued for an additional 12 days. By postoperative day 28, the defect's depth had significantly reduced such that the regenerating tissue was now approximately planar to the surrounding intact skin (**Figure 3E**), and a STSG was applied. At 1 week after STSG application, there was 100% graft take with no complications noted. Three weeks later, the defect was fully epithelialized with good tissue pliability (**Figure 3F**).

Discussion

Full-thickness wounds are commonly categorized and studied based upon wound etiology (eg, full-thickness burn, stage IV pressure injury, NSTI, and others). To the authors' knowledge, there is no existing term to group soft tissue defects based on wound bed complexity and depth regardless of the cause of initial defect. This void in nomenclature has prompted the authors to define the term "volumetric soft tissue defect" as a means to unify wounds of varying etiologies that share common features of irregular wound surface, depth that often includes the subcutaneous layers, exposed vital structures, and the high propensity for bacterial contamination (CDC grade 2 or higher).

The challenges with reconstruction of large volumetric soft tissue defects include the relative scale of these defects (depth and surface area); irregularity of the defect surface that may include undermining; presence of exposed vital structures that are prone to desiccation or necrosis; and frequent microbial contamination. Achieving rapid tissue infill of these defects and coverage of any exposed vital structures is the primary goal of reconstruction and has traditionally been approached with autologous tissue flaps. However, due to comorbidities, not all patients are suitable candidates for large autologous flap procedures,[28] and often the surgical

complexity of autologous tissue transfers brings a new set of challenges. Dermal matrices, like OFMs, are now an accepted part of the reconstructive ladder and facilitate the patient's own body to form a functional layer of well-vascularized tissue to provide coverage and fill the soft tissue defect. The use of dermal matrices was first proposed by Yannas and Burke,[29,30] who demonstrated clinically the use of a synthetic bilayer dermal matrix where the "artificial dermis resembles normal dermis and serves as a template for the synthesis of new connective tissue and the formation of a 'neodermis,' while it is slowly biodegraded." The development of dermal matrices enabled the advent of staged reconstructions to expedite definitive closure of complex tissue defects. Since these early studies the range of dermal matrices has ever expanded with new synthetic and naturally derived matrices being commercialized and adopted into clinical use. However, not all dermal matrices are the same with respect to clinical performance. For example, some synthetic dermal matrices are prone to infection or are relatively slow to integrate into the regenerating neodermis.[31] A subset of the available dermal matrices are naturally derived from human or animal tissue ECM. A key differential between ECM-based dermal matrices and their synthetic counterparts is a composition that includes naturally occurring proteins that exist in abundance in all soft tissues and are known to play key roles in soft tissue regeneration. ECM-based dermal matrices are known to rapidly vascularize and integrate into the regenerating neodermis and over time undergo a process of remodeling, mimicking the natural remodeling of ECM that occurs in all tissues.[32]

In this retrospective case series, there were a variety of volumetric soft tissue defects that included NSTIs, acute traumatic soft tissue injuries, and surgical wound dehiscence. There was a total of 13 defects included in this retrospective review where OFM matrix and/or morselized OFM were used to develop a healthy neodermis. In all cases, the defects were contaminated (CDC grade 2, or higher), and in 11 of the 13 cases, there was an exposed structure, including bone, surgical mesh, tendon, or viscera. The median time to complete integration of the graft and 100% granulation tissue formation was 21 days (mean, 23.4 ± 9.2 days). In 11 of the 13 defects, only a single application of OFM was required to regenerate a healthy neodermis. This is in contrast to the other available ECM-based surgical grafts where repeat applications are often necessary to achieve tissue infill of deep defects.[33,34]

One key goal of utilizing OFM in these volumetric defects is to restore the tissue depth and contour as close to anatomic normalcy as possible, as seen in **Figures 2E** and **3E**. This contour restoration can aid in maximizing function and cosmetic outcomes. Concurrent NPWT usage ranged from 3 to 8 weeks with a median of 4 weeks. Importantly, the authors found that the frequency of dressing changes (5-7 days) was reduced relative to the traditional frequency of 3 times per week.[35] This observation may have significant long-term impacts on the health economics of managing these complex defects by reducing the burden and costs associated with postoperative care of these patients. While reported costs vary, one publication estimated the mean theoretical cost of standard NPWT dressing change to be $94.01 per day,[36] so reducing the frequency of these dressing changes from 3 times per week to once per week is not insignificant. The use of ECM products adjunctively with NPWT to synergistically improve wound healing trajectory has been widely described in the scientific literature.[37-39] It has been postulated previously that collagen-based ECM products used concurrently with NPWT can enhance wound healing properties and shorten the duration of NPWT use.[40]

As previously discussed, the use of certain dermal matrices, including synthetic matrices, may result in higher rates of infection when placed in contaminated fields.[41,42] Infection rates seen for synthetic dermal matrices have been reported as high as 20%, 29.6%, and 18.1% in lower extremity reconstructions,[31] burns,[43] and trauma,[44] respectively. While methods to "milk" infection from these devices have been reported,[31] rates of graft loss as high as 20% have been reported in cases where this intervention was unsuccessful.[31] OFM is an intact ECM that is minimally processed to remove the ovine cells while maintaining ECM structure[45] and biology[46] with no chemical cross-linking that may otherwise inhibit the rate of neovascularization[47] and induce a proinflammatory tissue response.[48] In contrast to reports for synthetic dermal matrices,[42] we observed no infections in the current study, leading us to conclude that OFM is relatively resistant to infection and sufficiently robust to perform in a contaminated field.

Limitations

The current pilot study comprises observations from a single center with all the limitations of a retrospective case series. Not surprisingly, several of the patients included in the current report were lost to follow-up before complete closure of the volumetric defect (**Table 2**). This outcome, unfortunately, is entirely consistent with the high follow-up failure rate of trauma patients due to lack of insurance coverage, discharge to tertiary care facilities, and lack of patient education regarding the importance of follow-up care.[49-51] While the results of this case series are promising, there is a need for future research to expand the number of patients to validate these initial results. Future studies may involve a controlled study design, but this may be complicated by the absence of a "gold-standard" for the reconstruction of volumetric soft tissue defects.

Conclusions

This retrospective pilot case series builds on a growing body of evidence that OFM can be utilized to facilitate the formation of functional, well-vascularized soft tissue in large, contaminated, volumetric soft tissue defects. The OFM grafts were shown to complement NPWT and may reduce the frequency of dressing changes associated with NPWT usage in these complex soft reconstructive procedures.

Acknowledgments

The authors whish to acknowledge Aroa Biosurgery Limited for editorial assistance in preparing this manuscript. We thank the efforts of the nurses and surgical team of Northeast Georgia Medical Center.

Affiliations: [1]Northeast Georgia Medical Center, Department of Trauma and Acute Care Surgery, Gainesville, Georgia; [2]Aroa Biosurgery Limited, Auckland, New Zealand; [3]Northeast Georgia Medical Center, Northeast Georgia Physicians Group Vascular Center, Gainesville, Georgia

Correspondence: William M Vassy, MD; docvassy@icloud.com

Ethics: WCG Clinical provided institutional review board (IRB) services under work order 1-1572217-1. IRB approval was obtained on August 3, 2022. All patients provided written informed consent for their images and data to be used for research and publication purposes.

Disclosures: BAB and SGD are employees of Aroa Biosurgery Limited. WMV and MTC have received honoraria from Aroa Biosurgery Limited. No direct funding was received for this study.

References

1. Guest JF, Fuller GW, Vowden P. Costs and outcomes in evaluating management of unhealed surgical wounds in the community in clinical practice in the UK: a cohort study. *BMJ Open*. 2018;8(12):e022591. doi:10.1136/bmjopen-2018-022591

2. Flood MS, Weeks B, Anaeme KO, et al. Treatment of deep full-thickness wounds containing exposed muscle, tendon, and/or bone using a bioactive human skin allograft: a large cohort case series. *Wounds*. 2020;32(6):164-173.

3. Grogan BF, Hsu JR, Skeletal Trauma Research C. Volumetric muscle loss. *J Am Acad Orthop Surg*. 2011;19 Suppl 1:S35-7. doi:10.5435/00124635-201102001-00007

4. Sapino G, Lanz L, Roesti A, et al. One-stage coverage of leg region defects with STSG combined with VAC dressing improves early patient mobilisation and graft take: a comparative study. *J Clin Med.* 2022;11(12)doi:10.3390/jcm11123305

5. Sams HH, McDonald MA, Stasko T. Useful adjuncts to harvest split-thickness skin grafts. *Dermatol Surg*. 2004;30(12 Pt 2):1591-2. doi:10.1111/j.1524-4725.2004.30573.x

6. Um JH, Jo DI, Kim SH. New proposal for skin grafts on tendon-exposed wounds. *Arch Plast Surg.* 2022;49(1):86-90. doi:10.5999/aps.2021.00297

7. Kanchwala SK, Glatt BS, Conant EF, Bucky LP. Autologous fat grafting to the reconstructed breast: the management of acquired contour deformities. *Plast Reconstr Surg.* 2009;124(2):409-418. doi:10.1097/PRS.0b013e3181aeeadd

8. Kim TG, Choi MK. Secondary contouring of flaps. *Arch Plast Surg.* 2018;45(4):319-324. doi:10.5999/aps.2018.00542

9. Saber AY, Hohman MH, Dreyer MA. Basic flap design. Updated August 29, 2022. Accessed August 14, 2023. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK563252/

10. Zeiderman MR, Pu LLQ. Contemporary approach to soft-tissue reconstruction of the lower extremity after trauma. *Burns Trauma.* 2021;9:tkab024. doi:10.1093/burnst/tkab024

11. Schneeberger SJ, Kraft CT, Janis JE. No-touch technique of mesh placement in ventral hernia repair: minimizing postoperative mesh infections. *Plast Reconstr Surg.* 2020;145(5):1288-1291. doi:10.1097/PRS.0000000000006767

12. Cramer MC, Badylak SF. Extracellular matrix-based biomaterials and their influence upon cell behavior. *Ann Biomed Eng.* 2020;48(7):2132-2153. doi:10.1007/s10439-019-02408-9

13. Ousey KD, Djohan R, Dowsett C, et al. World Union of Wound Healing Societies consensus document. Surgical wound dehiscence: improving prevention and outcomes. February 20, 2018. Accessed August 14, 2023. Wounds UK. https://huddersfield.box.com/s/gw7grmclaxctndsuan3aydwt2qdkoown

14. Chaffin AE, Buckley MC. Extracellular matrix graft for the surgical management of Hurley stage III hidradenitis suppurativa: a pilot case series. *J Wound Care.* 2020;29(11):624-630. doi:10.12968/jowc.2020.29.11.624

15. Chaffin AE, Dowling SG, Kosyk MS, Bosque BA. Surgical reconstruction of pilonidal sinus disease with concomitant extracellular matrix graft placement: a case series. *J Wound Care.* 2021;30(Sup7):S28-S34. doi:10.12968/jowc.2021.30.Sup7.S28

16. Bosque BA, Frampton C, Chaffin AE, et al. Retrospective real-world comparative effectiveness of ovine forestomach matrix and collagen/ORC in the treatment of diabetic foot ulcers. *Int Wound J.* 2022;19(4):741-753. doi:10.1111/iwj.13670

17. Miller DL, Durden FL. Chest wall reconstruction utilizing ovine-derived reinforced tissue matrix. *Ann Thorac Surg.* 2023 May;115(5):1266-1272. doi:10.1016/j.athoracsur.2021.12.062

18. Ferzoco SJ. Early experience outcome of a reinforced Bioscaffold in inguinal hernia repair: a case series. *Int J Surg Open*. 2018;12:9-11. doi:10.1016/j.ijso.2018.06.001

19. Sawyer MAJ. New ovine polymer-reinforced bioscaffold in hiatal hernia repair. *JSLS.* Oct-Dec 2018;22(4): e2018.00057. doi:10.4293/JSLS.2018.00057

20. DeNoto G, Ceppa EP, Pacella SJ, et al. A prospective, single arm, multi-center study evaluating the clinical outcomes of ventral hernias treated with OviTex® 1S permanent reinforced tissue matrix: the BRAVO study 12-month analysis. *J Clin Med.* 2021;10(21):4998. doi:https://doi.org/10.3390/jcm10214998

21. Ankney C, Banaschak C, Sowers B, Szotek P. Minimizing retained foreign body in hernia repair using a novel technique: reinforced biologic augmented repair (ReBAR). *J Clin Med Res.* 2021;3(4):1-11. doi:https://doi.org/10.37191/Mapsci-2582-4333-3(4)-073

22. Sivaraj D, Henn D, Fischer KS, et al. Reinforced biologic mesh reduces postoperative complications compared to biologic mesh after ventral hernia repair. *Plast Reconstr Surg Glob Open.* Feb 2022;10(2):e4083. doi:10.1097/GOX.0000000000004083

23. DeNoto G. Bridged repair of large ventral hernia defects using an ovine reinforced biologic: a case series. *Ann Med Surg (Lond).* 2022;75:103446. doi:https://doi.org/10.1016/j.amsu.2022.103446

24. Timmer AS, Claessen JJM, Brouwer de Koning IM, et al. Clinical outcomes of open abdominal wall reconstruction with the use of a polypropylene reinforced tissue matrix: a multicenter retrospective study. *Hernia.* 2022;26(5):1241-1250. doi:10.1007/s10029-022-02604-y

25. Overbeck N, Nagvajara GM, Ferzoco S, May BCH, Beierschmitt A, Qi S. In-vivo evaluation of a reinforced ovine biologic: a comparative study to available hernia mesh repair materials. *Hernia.* 2020;24(6):1293-1306. doi:10.1007/s10029-019-02119-z

26. Negron L, Lun S, May BCH. Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. *Int Wound J.* 2012;11(4):392-397.

27. Zhao R, Liang H, Clarke E, Jackson C, Xue M. Inflammation in chronic wounds. *Int J Mol Sci.* 2016;17(12):2085. doi:10.3390/ijms17122085

28. Li D, Wang C, Wei W, et al. Postoperative complications of free flap reconstruction in moderate-advanced head and neck squamous cell carcinoma: a prospective cohort study based on real-world data. *Front Oncol.* 2022;12:792462. doi:10.3389/fonc.2022.792462

29. Yannas IV. Tissue regeneration by use of collagen-glycosaminoglycan copolymers. *Clin Mater*. 1992;9(3-4):179-187. doi:10.1016/0267-6605(92)90098-e

30. Yannas IV, Burke JF. Design of an artificial skin. I. Basic design principles. *J Biomed Mater Res.* 1980;14(1):65-81. doi:10.1002/jbm.820140108

31. Solanki NS, York B, Gao Y, Baker P, Wong She RB. A consecutive case series of defects reconstructed using NovoSorb Biodegradable Temporising Matrix: initial experience and early results. *J Plast Reconstr Aesthet Surg.* 2020;73(10):1845-1853. doi:10.1016/j.bjps.2020.05.067

32. Bohn GA, Chaffin AE. Extracellular matrix graft for reconstruction over exposed structures: a pilot case series. *J Wound Care.* 2020;29(12):742-749. doi:10.12968/jowc.2020.29.12.742

33. Stone R, 2nd, Saathoff EC, Larson DA, et al. Accelerated wound closure of deep partial thickness burns with acellular fish skin graft. *Int J Mol Sci.* 2021;22(4):1590. doi:10.3390/ijms22041590

34. Schlanser V, Dennis A, Ivkovic K, et al. Placenta to the rescue: limb salvage using dehydrated human amnion/chorion membrane. *J Burn Care Res.* 2018;39(6):1048-1052. doi:10.1093/jbcr/irx031

35. Norman G, Goh EL, Dumville JC, et al. Negative pressure wound therapy for surgical wounds healing by primary closure. *Cochrane Database Syst Rev.* 2020;6:CD009261. doi:10.1002/14651858.CD009261.pub6

36. Kim JJ, Franczyk M, Gottlieb LJ, Song DH. Cost-effective alternative for negative-pressure wound therapy. *Plast Reconstr Surg Glob Open.* 2017;5(2):e1211. doi:10.1097/GOX.0000000000001211

37. Fleming ME, O'Daniel A, Bharmal H, Valerio I. Application of the orthoplastic reconstructive ladder to preserve lower extremity amputation length. *Ann Plast Surg.* 2014;73(2):183-9. doi:10.1097/SAP.0b013e3182a638d8

38. Dillingham CS, Jorizzo J. Managing ulcers associated with pyoderma gangrenosum with a urinary bladder matrix and negative-pressure wound therapy. *Adv Skin Wound Care.* Feb 2019;32(2):70-76. doi:10.1097/01.ASW.0000546120.32681.bc

39. Gabriel A, Gollin G. Management of complicated gastroschisis with porcine small intestinal submucosa and negative pressure wound therapy. *J Pediatr Surg.* 2006;41(11):1836-1840. doi:10.1016/j.jpedsurg.2006.06.050

40. Sreelesh LS, Laxminarayan Bhandari P. An easy technique for negative-pressure wound therapy for extremities using collagen powder and sterile gloves. *Indian J Surg.* 2017;79(1):81-83. doi:10.1007/s12262-017-1589-z

41. Li H, Lim P, Stanley E, et al. Experience with NovoSorb® Biodegradable Temporising Matrix in reconstruction of complex wounds. *ANZ Journal of Surgery.* 2021;91(9):1744-1750. doi:10.1111/ans.16936

42. Gonzalez SR, Wolter KG, Yuen JC. Infectious complications associated with the use of Integra: a systematic review of the literature. *Plast Reconstr Surg Glob Open.* 2020;8(7):e2869. doi:10.1097/GOX.0000000000002869

43. Bargues L, Boyer S, Leclerc T, Duhamel P, Bey E. [Incidence and microbiology of infectious complications with the use of artificial skin Integra in burns]. *Ann Chir Plast Esthet.* Dec 2009;54(6):533-539. doi:10.1016/j.anplas.2008.10.013

44. Huang SR, Liu JT, Zhang Y, Ouyang RL, Ruan MZ, Luo B. [Repair of complex wounds on hands after burns or trauma]. *Zhonghua Shao Shang Za Zhi*. 2019;35(5):362-366. doi:10.3760/cma.j.issn.1009-2587.2019.05.007

45. Sizeland KH, Wells HC, Kelly SJR, et al. Collagen fibril response to strain in scaffolds from ovine forestomach for tissue engineering. *ACS Biomater Sci Eng*. 2017;3(10):2550-2558. doi:10.1021/acsbiomaterials.7b00588

46. Dempsey SG, Miller CH, Hill RC, Hansen KC, May BCH. Functional insights from the proteomic inventory of ovine forestomach matrix. *J Proteome Res*. 2019;18(4):1657-1668. doi:10.1021/acs.jproteome.8b00908

47. Mestak O, Spurkova Z, Benkova K, et al. Comparison of cross-linked and non-cross-linked acellular porcine dermal scaffolds for long-term full-thickness hernia repair in a small animal model. *Eplasty*. 2014;14:e22.

48. Delgado LM, Bayon Y, Pandit A, Zeugolis DI. To cross-link or not to cross-link? Cross-linking associated foreign body response of collagen-based devices. *Tissue Eng Part B Rev*. 2015;21(3):298-313. doi:10.1089/ten.TEB.2014.0290

49. Stone ME, Jr., Marsh J, Cucuzzo J, Reddy SH, Teperman S, Kaban JM. Factors associated with trauma clinic follow-up compliance after discharge: experience at an urban Level I trauma center. *J Trauma Acute Care Surg*. 2014;76(1):185-190. doi:10.1097/TA.0b013e3182aafcd5

50. Overton TL, Shafi S, Gandhi RR. Local access to care programs increase trauma patient follow-up compliance. *Am J Surg*. 2014;208(3):476-479. doi:10.1016/j.amjsurg.2013.11.008

51. Leukhardt WH, Golob JF, McCoy AM, Fadlalla AM, Malangoni MA, Claridge JA. Follow-up disparities after trauma: a real problem for outcomes research. *Am J Surg*. 2010;199(3):348-352; discussion 353. doi:10.1016/j.amjsurg.2009.09.021

Ovine Forestomach Matrix in the Surgical Management of Complex Lower-Extremity Soft-Tissue Defects

A Retrospective Multicenter Case Series

Brandon A. Bosque, DPM*
Shane G. Dowling, MSPAS*
Barnaby C.H. May, PhD*
Richard Kaufman, DPM†
Igor Zilberman, DPM‡
Nooshin Zolfaghari, DPM‡
Howie Que, DPM§
James Longobardi, DPM§
Joseph Skurka, DPM||
James E. Geiger, Jr., DPM ¶
M. Mark Melin, MD#

Background: Chronic lower-extremity defects may lead to major amputations and have severe consequences on patient quality of life and mortality. Dermal matrices have become part of the reconstructive ladder and are often deployed in these scenarios to quickly build neodermis, especially in volumetric defects over exposed bone and tendon initially, to allow for subsequent closure by means of split-thickness skin grafting (STSG) or secondary intention. Ovine forestomach matrix (OFM) is a decellularized extracellular matrix (ECM) bioscaffold available in both sheet and particulate forms that can be used as a dermal matrix in various soft-tissue reconstruction procedures.

Methods: This retrospective case series evaluated the use of OFM products in the surgical reconstruction of 50 cases (n = 50) comprised of challenging lower-extremity defects from seven healthcare centers. Patient records were reviewed to identify comorbidities, defect cause, defect size, presence of exposed structures, Centers for Disease Control and Prevention contamination score, Wagner grade, OFM graft use, time to 100% granulation tissue, STSG use, overall time to heal, and postoperative complications. The primary study outcomes were time (days) to 100% granulation tissue formation, with secondary outcomes including overall time to wound closure (weeks), STSG take at 1 week, and complications.

Results: The results of this case series demonstrate OFM as a clinically effective treatment in the surgical management of complex lower-extremity soft-tissue defects with exposed structures in patients with multiple comorbidities. One application of OFM products was effective in regenerating well-vascularized neodermis, often in the presence of exposed structures, with a mean time to 100% granulation of 26.0 $\pm$ 22.2 days.

Conclusions: These data support the use of OFM as a safe, cost-effective, and clinically effective treatment option for coverage in complex soft-tissue wounds, including exposed vital structures, and to shorten the time to definitive wound closure in complicated patient populations. (J Am Podiatr Med Assoc 113(3), 2023)

*Aroa Biosurgery, Research and Clinical Development, San Diego, CA.
†Ankle and Foot Centers of America, Roswell, GA.
‡Memorial Hospital Pembroke, Davie, FL.
§Scripps Mercy Hospital, Chula Vista, CA.
||Ephraim McDowell Regional Medical Center, Danville, KY.
¶Northwestern Medicine–Palos Hospital, Palos Heights, IL.
#M Health Fairview Wound Healing Institute, Edina, MN.

Corresponding author: Brandon A. Bosque, DPM, Aroa Biosurgery, Research and Clinical Development, 9155 Brown Deer Rd #2 San Diego, CA 92121. (E-mail: brandon.bosque@aroa.com)

Standard wound care, often along with adjunctive therapies (eg, negative-pressure wound therapy [NPWT], cellular tissue products) is the first-line intervention for lower-extremity soft-tissue defects. However, many cases may be complicated by additional factors, such as the presence of a deep infection that warrants immediate surgical intervention to reconstruct the defect and provide closure.[1] Lower-extremity defects can be challenging to manage effectively regardless of underlying cause and, when not adequately addressed, can lead to lower-limb amputation and an increased mortality rate. For example, lower-limb necrotizing soft-tissue infections (NSTIs) have a mortality rate of 25% to 35%.[2] These defects are complex when volumetric tissue loss is involved, resulting in complex soft-tissue wounds that often result in revealing denuded vital structures such as bone, tendon, nerve, and/or vasculature. Exposure of vital structures can lead to desiccation, necrosis, progressing infection, and severe long-term functional consequences.[3]

Lower-extremity defects present a reconstructive challenge to surgeons in terms of closure, preservation of function, and cosmetic outcomes.[2] Denuded and devitalized critical structures often lack sufficient vascularization and sof-tissue extracellular matrix (ECM) to support immediate coverage with a split-thickness skin graft (STSG) and therefore require surgical techniques that facilitate coverage and closure. Traditionally, this has been achieved through the use of local or free flap procedures to provide immediate coverage to the exposed vital structures once any infection has been addressed.[4] However, flap-based reconstructions can lead to lengthy operating times, introduce the risk of donor-site morbidity, and have the potential for flap failure.[5] Dermal matrices, among other surgical procedures, have filled a need in lower-limb reconstruction where traditional local or free flap procedures are not possible.[6] The use of a dermal matrix negates the risks associated with morbidity of the donor/harvest site and may decrease surgical complexity associated with local or free flap procedures. There are now a wide range of dermal matrices that are commercially available and include synthetic and tissue-derived technologies.[6] Tissue-derived products are typically manufactured from a suitable mammalian tissue source that is processed to isolate and decellularize the tissue ECM.[7] Unlike purely synthetic dermal matrices, decellularized ECM (dECM) products (sometimes referred to as "biologics") when processed properly, retain many of the biological components of tissue ECM that are known to aid tissue regeneration.[8,9] These types of products are now an integral part of the reconstructive ladder, and are especially useful where the soft-tissue defect is further complicated by microbial contamination, poor vascularity, or local chronic inflammation.[6] Like synthetic dermal matrices, dECM products provide a scaffold for cell infiltration, proliferation, and neovascularization, leading to neodermis formation and integration of the naturally occurring and preserved scaffold inherent in the source from which it was derived. Once the neodermis has been formed, definitive closure can be accomplished with a STSG, or closure by means of secondary intention. One common barrier to the adoption of dECM products tends to be limited accessibility because of relatively high product costs. However, relative to flap-based procedures, the overall surgical costs may be reduced using dECM products because of decreased surgical time and length of patient hospitalization.[5]

Various dECM grafts are clinically available that differ in the source tissue (eg, human, porcine, bovine, equine) and processing technique to decellularize the tissue.[10] Ovine forestomach matrix (OFM) is a dECM isolated from juvenile (<12 months) sheep forestomach and comprises the propria-submucosa tissue layer that has undergone decellularization, lyophilization, and terminal sterilization.[11] Ovine forestomach matrix–based products have been shown to be effective in chronic wounds,[12-15] plastic and reconstructive procedures,[16-19] and general surgery procedures.[20-23] Ovine forestomach matrix–based products have found a particular niche in the regeneration of soft tissues in patients who would otherwise experience compromised healing or are at risk for postoperative complications because of the presence of bacterial contamination, local chronic tissue inflammation, or patient comorbidities. Healing in these challenging environments may be aided by the inherent preserved biological components of OFM,[24] which have been shown to be anti-inflammatory,[25,26] stimulate angiogenesis,[27] and recruit mesenchymal stem cells.[28]

For reconstructive surgical procedures, OFM is available as a 2-, 3-, or 5-layer graft (Myriad Matrix; Aroa Biosurgery Limited, Aukland, New Zealand). The multilayer OFM graft is fabricated using a novel manufacturing process that retains the structure and biology of the dECM material, without introducing any additional components (eg, synthetic materials or crosslinked collagen).[29] The resultant OFM graft enables rapid cell infiltration by means of the porous architecture of OFM, but also by means of engineered pores and remnant vascular channels

that allow for vertical and transverse cell migration into the graft. Previous in vivo studies and histologic assessments have demonstrated the rapid cell infiltration, and neovascularization of multilayered OFM grafts.[30] More recently, a particulate format of OFM has been commercially available for applications in soft-tissue repair (Myriad Morcells; Aroa Biosurgery Limited). The particulate, or "morselized," format was designed to provide rapid biology to the wound bed and enables intimate contact with irregular wound surfaces compared to the sheet form. Given the previously reported performance of OFM in a range of inflammatory soft-tissue defects (eg, pilonidal sinus, hidradenitis suppurativa, chronic wounds), the following retrospective multicenter case series was undertaken to evaluate the performance of OFM graft, particulate products, or both in complex lower-extremity reconstructions that would otherwise be at risk of complications, such as infection or limb amputation.

Methods

The study protocol was evaluated by the Advarra Institutional Review Board (Columbia, Maryland) and ethical oversight of the retrospective study was waived. The study was conducted in accordance with institutional guidelines and the World Medical Association Declaration of Helsinki ethical guidelines. All patient information, including any patient images, were deidentified.

Data were collected from patients who met the inclusion and exclusion criteria (Table 1) and represented patients who had undergone inpatient lower-extremity reconstruction using OFM products between January of 2019 and December of 2021. Ovine forestomach matrix–graft (Myriad Soft Tissue Matrix) and OFM particulate (Myriad Morcells) were used according to the instructions for use. The selection of either product was at the discretion of the attending surgeon at the time of the procedure and included cases that had used either OFM graft or OFM particulate, or both products in combination. Cases included patients who had received an STSG, or those who underwent closure by means of secondary intention at the discretion of the attending physician (Fig. 1). The primary study endpoint was median time to 100% granulation (days) of the graft (Fig. 1). Secondary endpoints included median time to closure (weeks); percentage STSG take at 1 week (if applicable); and adverse events (including hematoma/seroma, dehiscence, infection, and recurrence). All data were collated in Excel (Microsoft Corp, Redmond, Washington). Descriptive statistics (mean, median, and standard error) were computed using GraphPad Prism (Version 9.0.0; GraphPad Software, LLC, San Diego, California).

Table 1. Inclusion and Exclusion Criteria

Inclusion
Male or female patients aged 18 years or older
Patients with a lower-extremity soft-tissue defect treated with OFM graft or OFM particulate as part of their surgical intervention
Exclusion
Patients still under active management
Patients who did not receive OFM graft or OFM particulate as part of their lower-extremity soft-tissue reconstruction

Abbreviation: OFM, ovine forestomach matrix.

Results

A total of 50 patients from seven sites were enrolled in the study having met the inclusion and exclusion criteria (Table 1). Median patient age was 63.0 years (mean, 60.6 ± 15.2 years; range, 28–87 years), with 54% of patients being male and 46% of patients being female (Table 2). Patient comorbidities included diabetes mellitus type 1 (2%), diabetes mellitus type 2 (66%), hypertension (34%), peripheral arterial disease (54%), peripheral veneous disease (80%), lymphedema (22%), atrial fibrillation/anticoagulant therapy (12%), and coronary artery disease (8%). Twenty-four percent of patients were previously diagnosed with four of the comorbidities captured in the study (Table 2). A significant proportion of all defects were classified as diabetic foot ulcers (DFUs) (48%) and of the DFUs, half were complicated by a necrotizing soft-tissue infection (50%) (Table 3). Of all defects included in the study, 34% had exposed bone, 10% had exposed tendon, 18% had both exposed tendon and bone, and 4% had exposed capsule (Table 3). Only 34% of the defects presented with no exposed structures. Where applicable, Wagner grades were recorded as grade 2 (8%), grade 3 (18%), and grade 4 (22%), and all defects had a Centers for Disease Control and Prevention contamination score of IV. Osteomyelitis was reported in 54% of cases. The median age of the defects was 5.5 weeks (mean, 60.0 ± 152.5 weeks; range, 0–780 weeks), and the median defect area was 40 cm^2 (mean, 84.2 ± 106 cm^2; range, 4–429 cm^2). The median wound depth was 0.3 cm (mean, 10.6 ± 0.9 cm; range, 0.1–5.0 cm).

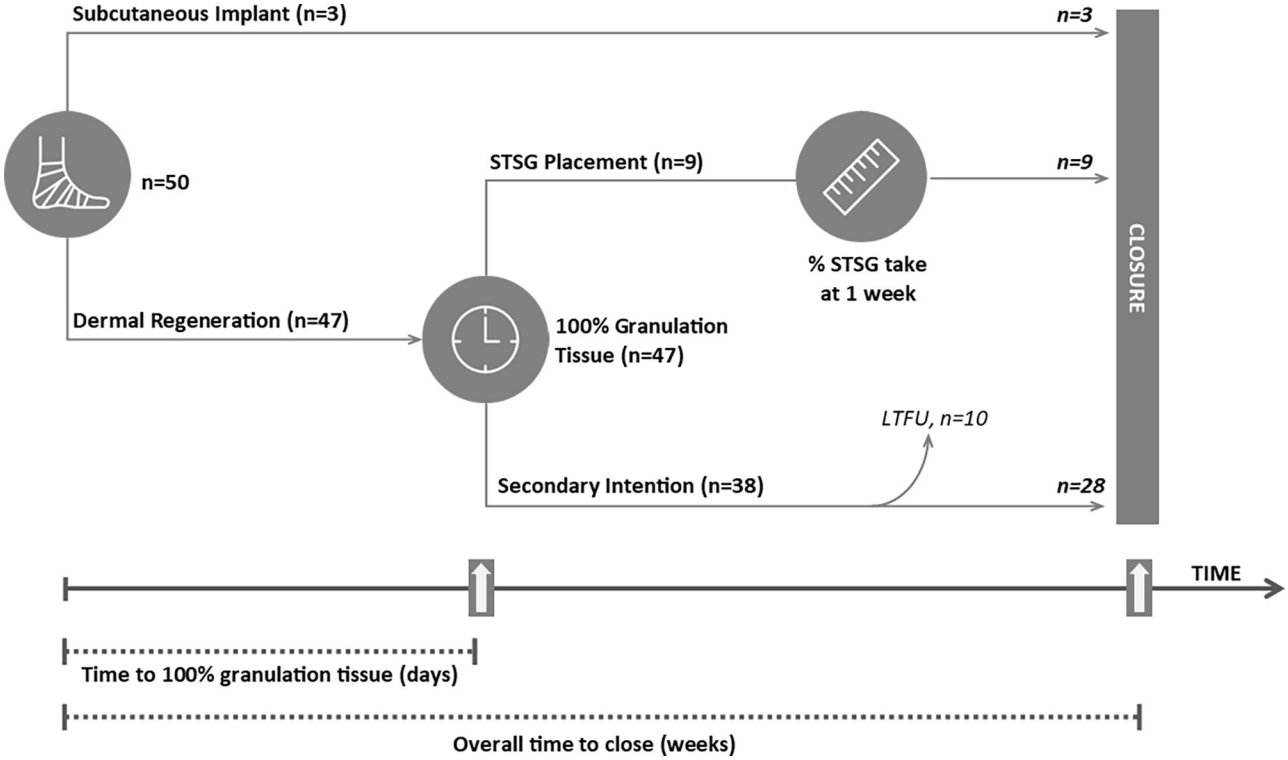


Figure 1. Retrospective study design and outcome measures. LTFU, loss to follow-up; STSG, split thickness skin graft; n, sample size.

Forty-one patients (82%) received OFM graft, whereas three patients (6%) received OFM particulate, and six patients (12%) received both (Table 4). The OFM graft was used as an implant to reinforce a flap in three patients. Median product use was 1.0 application (mean, 1.0 ± 0.1 application). Eighteen patients (36%) received postoperative NPWT, with a median NPWT treatment duration of 3.8 weeks (mean, 4.4 ± 2.5 weeks; range, 1–10 weeks).

Ten patients were lost to follow-up before complete closure of the defect, but after 100% granulation tissue had formed (Fig. 1). Where OFM products were used for dermal regeneration (n = 47), the median time to 100% granulation tissue was 17 days (mean, 26 ± 22.2 days; range, 7–120 days) (Table 5). Nine patients received an STSG as part of a two-stage reconstruction procedure. Of the patients who received an STSG, the median percentage STSG take at 1 week was 75% (mean, 74.6 ± 18%; range, 50–100%). Thirty-eight patients (76%) were closed by means of secondary intention, with an overall median time to close of 14 weeks (mean, 14.0 ± 5.9 weeks; range, 1–27 weeks) (Table 5 and Fig. 2). The overall time to closure (from the initial surgical procedure to closure) across defects (n = 40) was 13 weeks (mean, 13.7 ± 6.9 days; range, 2–29 weeks). A subgroup analysis based on surgical type (dermal regeneration, implant) and closure type (STSG or secondary intention) showed mean overall time to closure of 3.3 ± 2.3 weeks, 11.2 ± 6.4 weeks, and 15.6 ± 6.2 weeks for procedures using OFM graft as an implant, defects closed by means of STSG, and those closed through secondary intention, respectively (Table 5). No postoperative complications were reported across the cohort; specifically, no cases of infected OFM that required early graft removal or surgical-site infection (SSI) were reported (Table 5).

Case Reports

Case 1

A 28-year-old man with a significant medical history of diabetes mellitus type 1 presented with an NSTI of the left fifth digit and metatarsal (Fig. 3A). The patient was taken to the operating room for a resection of the fifth digit and metatarsal. The resulting soft-tissue defect was approximately 10 × 8 × 1 cm, with exposed extensor tendons and metatarsal bone (Fig. 3B). The defect was then dressed with a

Table 2. Patient Demographics

Characteristic	Value
No. of participants	50
Sex (No. [%])	
Male	27 (54)
Female	23 (46)
Participant age (years)	
Mean ± SD	60.6 ± 15.2
Median	63.0
Comorbidities (No. [%])	
DM1	1 (2)
DM2	33 (66)
HTN	17 (34)
PAD	27 (54)
PVD	40 (80)
Afib/anticoagulants	6 (12)
CAD	4 (8)
Cancer	3 (6)
Lymphedema	11 (22)
No. of comorbidities (No. [%])	
1	5 (10)
2	18 (36)
3	11 (22)
4	12 (24)
5	4 (8)

Abbreviations: Afib, atrial fibrillation; CAD, coronary artery disease; DM1, type 1 diabetes mellitus; DM2, type 2 diabetes mellitus; HTN, hypertension; PAD, peripheral arterial disease; PVD, peripheral vascular disease; SD, standard deviation of the mean.

nonadherent layer and NPWT at 125 mm Hg. The patient was then taken back to the operating room 72 hours later for reconstruction of the defect. A five-layer OFM graft was applied to the wound bed and secured to the wound perimeter with surgical staples (Fig. 3C). The wound was then dressed with a nonadherent contact layer and NPWT at 125 mm Hg. The patient was discharged to home with a 1-week postoperative follow-up. At the 1-week visit, the graft was 100% granulated with complete coverage of the exposed bone and tendons (Fig. 3D). The patient was taken back to the operating room the following week for application of an STSG. At 1 week after STSG application, there was 90% take of the graft with a small portion on the distal STSG lost (Fig. 3E). The STSG was epithelializing between the interstices and there were no complications. At the patient's 8-week follow-up, the wound was fully healed with pliable soft tissue (Fig. 3F). The patient was back to walking in an orthotic shoe with no recurrence to 6-month follow-up.

Case 2

A 52-year-old man with a significant medical history of diabetes mellitus type 1, peripheral vascular disease, and Charcot neuroarthropathy had previously undergone (4 weeks prior) a Charcot foot reconstruction consisting of a triple-joint arthrodesis and medial column fusion with internal and external fixation. Subsequently, the patient had a surgical dehiscence with exposed bone and joint of the right foot (Fig. 4A). The patient was treated with intravenous antibiotics and taken back to the operating room for surgical debridement of nonviable tissue. Ovine forestomach matrix particulate (1,000 mg) was hydrated with the patient's blood and packed into the defect over the exposed bone and joint space (Fig. 4B). A three-layer OFM graft was applied to the superficial defect overlying the OFM particulate and secured with nonabsorbable

Table 3. Baseline Defect Characteristics

Characteristic	Value
Defect age (weeks)	
Mean ± SD	60.0 ± 152.5
Median	5.5
Baseline defect area (cm^2)	
Mean ± SD	84.2 ± 106.0
Median	40.0
Baseline maximum defect depth (cm)	
Mean ± SD	0.6 ± 0.9
Median	0.3
Defect type (No. [%])	
Surgical dehiscence	5 (10)
Traumatic	5 (10)
Pyoderma gangrenosum	1 (2)
Burn	2 (4)
DFU	24 (48)
NSTI	12 (50)
Calciphylaxis	1 (2)
Mixed vascular ulcer	1 (2)
VLU	10 (20)
Arterial ulcer	1 (2)
Exposed structures (No. [%])	
None	17 (34)
Bone	17 (34)
Tendon	5 (19)
Bone and tendon	9 (18)
Capsule	2 (4)
Wagner grade (n = 24) (No. [%])	
1	—
2	4 (8)
3	9 (18)
4	11 (22)
CDC contamination score (No. [%])	
I	—
II	—
III	—
IV	50 (100)
Osteomyelitis (No. [%])	
Yes	27 (54)

Abbreviations: DFU, diabetic foot ulcer; NSTI, necrotizing soft-tissue infection; SD, standard deviation of the mean; VLU, venous leg ulcer.

Table 4. Use and Product Type

Characteristic	Value
Use type (No. [%])	
Implantation	3 (6)
Dermal regeneration	47 (94)
Product type (No. [%])	
OFM graft only	41 (82)
Three-layer	6 (15)
Five-layer	35 (85)
OFM particulate only	3 (6)
OFM graft and particulate	6 (12)
Three-layer	—
Five-layer	6 (100)
Product use	
Mean ± SD	1.0 ± 0.1
Median	1.0
NPWT duration (No. [%])	18 (36)
Mean ± SD (weeks)	4.4 ± 2.5
Median (weeks)	3.8

Abbreviations: NPWT, negative-pressure wound therapy; OFM, ovine forestomach matrix; SD, standard deviation of the mean.

sutures. The wound was treated with NPWT (125 mm Hg). The patient was discharged to a skilled nursing facility with weekly follow-up on an outpatient basis. At week 1, the OFM graft appeared viable, with no evidence of infection or other surgical complications (Fig. 4C). At week 2, the wound bed was 100% filled with viable granulation tissue, with no further exposed bone or joint. The patient was returned to the operating room for removal of the external fixator, and a second application of three-layer OFM graft was performed, as the patient was not deemed to be a good candidate for STSG. The hardware removal necessitated a return to the operating room regardless of the wound progress. Negative-pressure wound therapy (125 mm Hg) was continued. Two weeks after the second procedure, residual OFM was sharply debrided, revealing viable vascularized tissue filling the defect (Fig. 4D). The wound was closed by means of secondary intention with weekly application of one-layer OFM (Endoform; Aroa Biosurgery Limited). By 10 weeks after the index surgery, the wound bed was 80% epithelialized (Fig. 4E), and at the 12-week postoperative visit, the wound was fully healed (Fig. 4F). The patient suffered no complications from the procedure and was able to walk following healing and removal of the external fixator. There was no recurrence out to the last follow-up at 18 weeks.

Table 5. Study Outcomes

Characteristic	Value
Days to 100% granulation tissue	
No. (%)	47 (94)
Mean ± SD (days)	26.0 ± 22.2
Median (days)	17.0
% STSG take at 1 week	
No. (%)	9 (94)
Mean ± SD	74.6 ± 18.0
Median (%)	75.0
Time to close	
All participants	
No. (%)	40 (80)
Mean ± SD (weeks)	13.7 ± 6.9
Median (weeks)	13.0
Implant	
No. (%)	3 (6)
Mean ± SD (weeks)	3.3 ± 2.3
Median (weeks)	2.0
STSG	
No. (%)	9 (18)
Mean ± SD (weeks)	11.2 ± 6.4
Median (weeks)	9.0
Secondary intention	
No. (%)	28 (56)
Mean ± SD (weeks)	15.6 ± 6.2
Median (weeks)	16.0

Abbreviations: SD, standard deviation of the mean; STSG, split-thickness skin graft.

Case 3

A 70-year-old woman with a significant medical history of diabetes mellitus type 1, peripheral vascular disease, and gangrene resulting in multiple digital amputations of the left foot had recently undergone (4 weeks prior) a transmetatarsal amputation (TMA). The patient presented to the hospital with surgical dehiscence of the TMA site with a concomitant cellulitis infection. The patient was treated

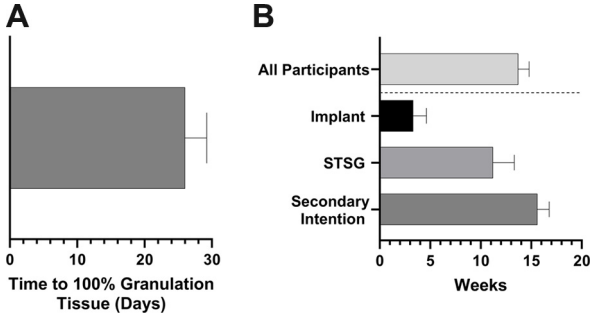


Figure 2. Study outcomes. A, Time to 100% granulation tissue. Error bars represent standard error of the mean (n = 47). B, Overall time to heal. Error bars represent standard error of the mean. All participants, n = 40; implant, n = 3; split-thickness skin graft (STSG), n = 9; secondary intention, n = 28.

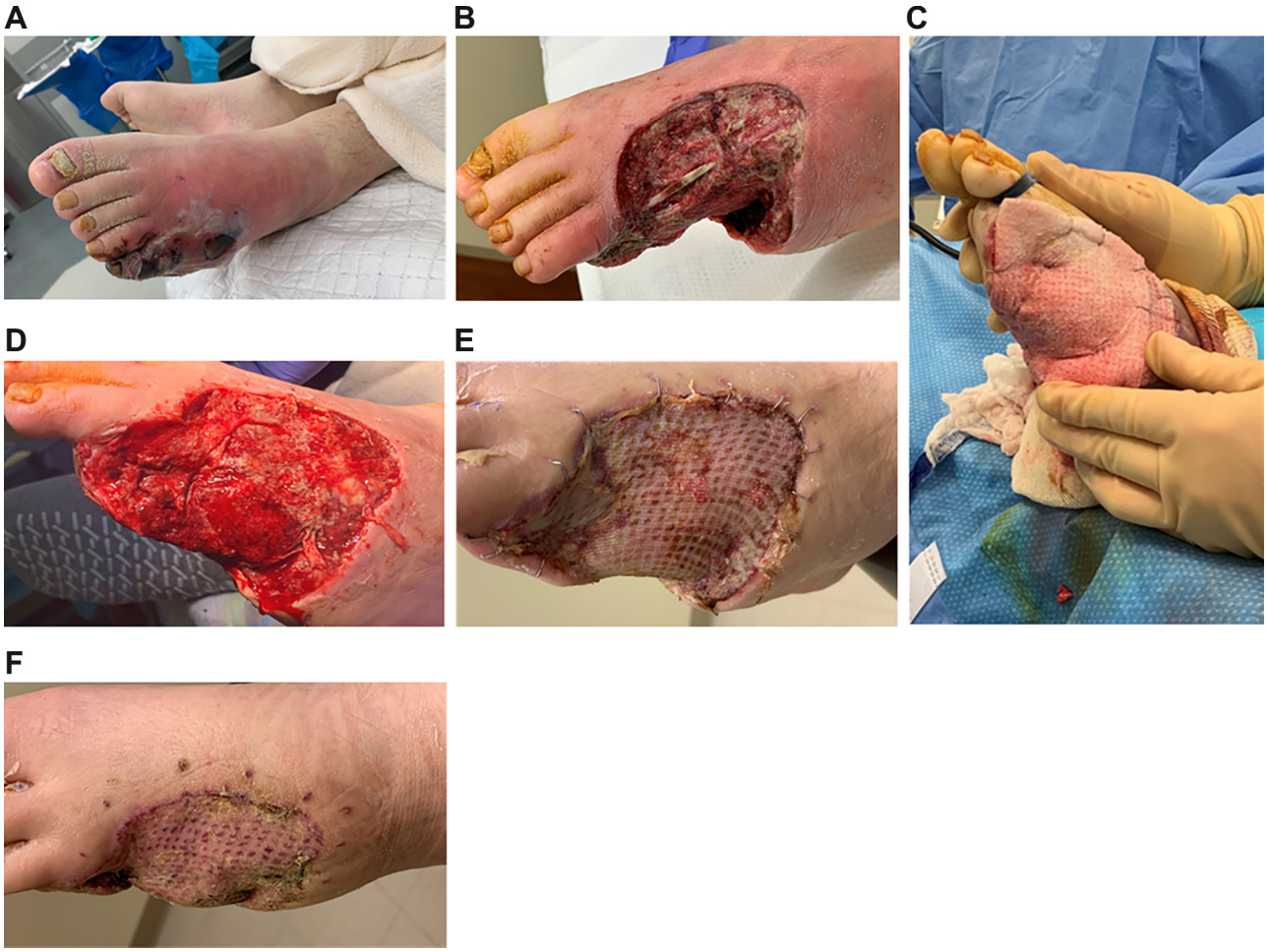


Figure 3. A, Necrotizing soft-tissue infection of the left fifth digit and metatarsal on presentation. B, After resection of necrotic tissue. C, Ovine forestomach matrix five-layer graft placement. D, One week postoperatively. E, One week after split-thickness skin graft placement. F, Eight-week postoperative follow-up.

with intravenous antibiotics and taken to the operating room for a revision TMA, resulting in further bone and soft-tissue resection at the site. A five-layer OFM graft was hydrated with sterile saline solution, applied over the exposed bone and soft tissue of the TMA site, and secured to the wound bed with absorbable sutures (Fig. 5A). A layered surgical closure was performed to implant the OFM graft, with a skin closure by means of nonabsorbable sutures (Fig. 5B). The wound was dressed with nonadherent and foam dressings. The patient was discharged to home with oral antibiotics and instructed to follow-up 1 week postoperatively. At 2 weeks, the flap was found to be viable, with the skin edges healing well. The wound was fully healed by week 3 and there was no evidence of infection or dehiscence noted at the 2-month follow-up.

Discussion

Patients included in this multicenter retrospective study presented with a typical range of lower-extremity defects requiring surgical intervention, and all patients had compromised healing potential and an elevated risk for amputation because of significant comorbidities (Table 2). Most cases (66%) were further complicated by exposed vital structures (ie, bone, tendon, capsule), that would otherwise have presented a challenge to immediate closure by means of STSG. Dermal matrices, whether synthetic or biologic, are typically used to regenerate neodermis in deep partial- or full-thickness defects before STGS placement or to accelerate closure by means of secondary intention. As such, the primary study endpoint was time to granulation of the OFM graft, rather than time to

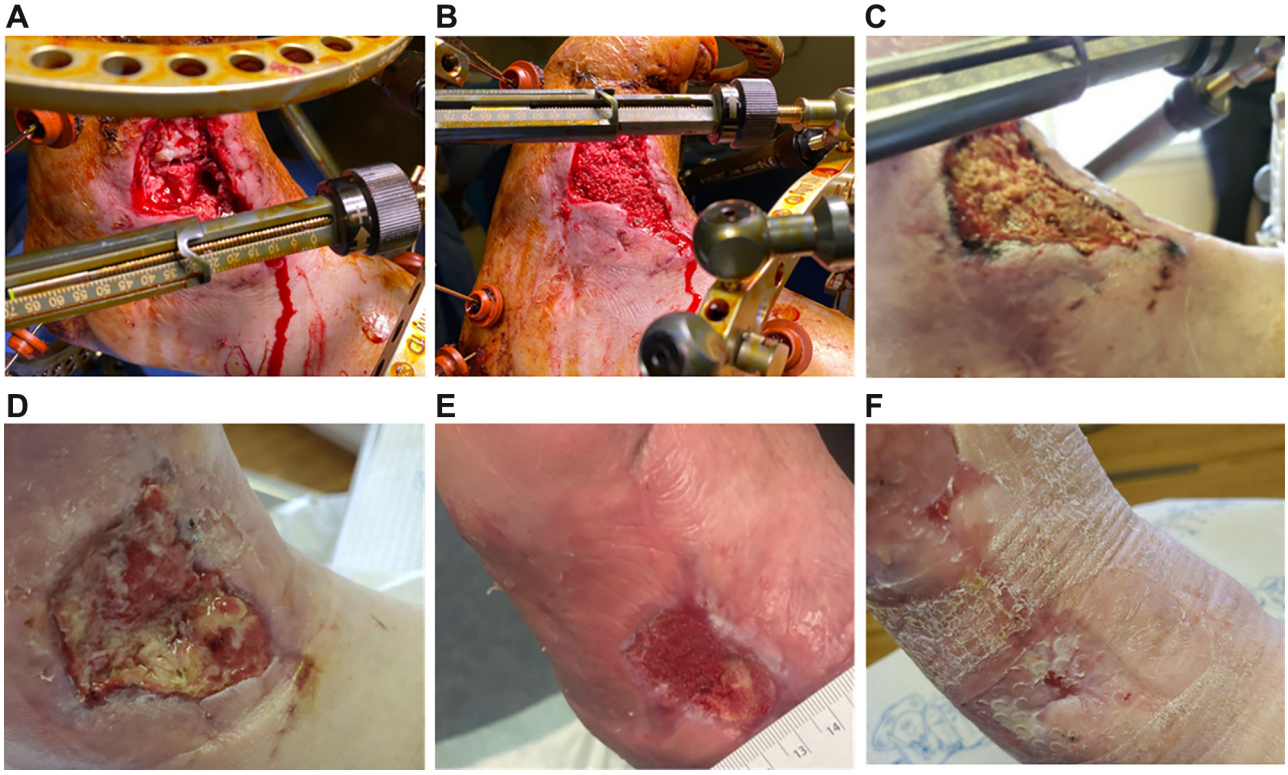


Figure 4. A, Initial wound after surgical dehiscence from Charcot reconstruction. B, Ovine forestomach matrix particulate placed directly over exposed bone and joint. C, One week postoperatively. D, Two weeks postoperatively from second ovine forestomach matrix graft placement. E, Ten weeks postoperatively, 80% epithelialized. F, Twelve weeks postoperatively, fully epithelialized.

complete wound closure. Across the 50 patients, the median time to 100% granular neodermis was 26 days. This is comparable to the median time to granulation tissue observed with use of other dermal matrices. Li et al[31] reported a median time to granulation of approximately 36 days (range, 15–81 days) in a retrospective case series of 35 complex wounds, including 14 lower-extremity wounds using a polyurethane biodegradable temporizing matrix. Studies using a bilayered dermal matrix in lower-limb reconstruction have reported times to graft integration of 14 to 28 days[32] and 21 days.[33]

As is commonly seen in these types of lower-extremity defects, bacterial contamination was a potential challenge across all patients, with Centers for Disease Control and Prevention contamination grades of IV, and 54% of patients having underlying osteomyelitis. Furthermore, 50% of DFUs required reconstruction because of an NSTI. Across the 12 cases that included an NSTI, there were no instances of SSI or graft loss because of infection. This finding is consistent with clinical studies using OFM-based devices for complex hernia repair of contaminated defects where the rates of SSI and other complications were low.[20,23] This is in contrast to synthetic dermal matrices where infection and infection-related complications (eg, graft loss) are often reported. In some instances, these synthetic dermal matrices result in containment of purulent exudate if the graft becomes infected, requiring "milking" or removal of the matrix.[34] One synthetic dermal matrix was cited by Solanki et al[34] to "avoid its use in the foot and ankle region in patients with peripheral vascular disease . . . as they are at high risk of [biodegradable temporizing matrix graft] failure." In a 2020 systematic review of over 3,500 articles, 26 articles were found to have reported infection rates when collagen-glycosaminoglycan biodegradable matrix grafts (Integra Bilayer Wound Matrix [IBWM]; Integra LifeSciences Corp, Plainsboro, New Jersey) were used. The meta-analysis of those 26 articles revealed infections in 212 of the 1,254 wounds treated with IBWM (16.9%).[35] Furthermore, one retrospective case series of nonhealing soft-tissue defects of the lower extremity that were treated with IBWM found a 17.6% infection rate.[36] These infections have been reported to be

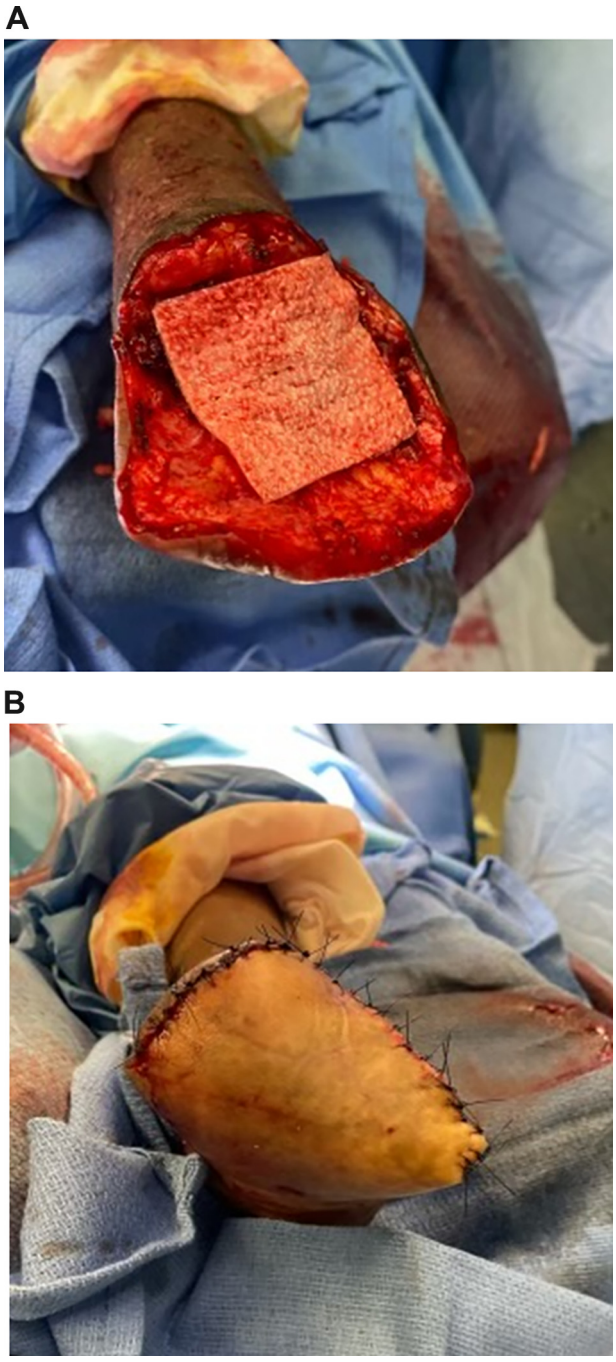


Figure 5. A, Intraoperative photographs after resection with placement of ovine forestomach matrix five-layer graft. B, Skin surgical closure with nonabsorbable sutures.

associated with higher graft failure[35] and highlights the established fact that IBWM requires an uncontaminated wound bed for success.[37] The differences between synthetic grafts mentioned above compared to OFM graft may be attributed to the beneficial biological components found in OFM.[24] Previous studies have described antibacterial properties of dECM scaffolds, acting to quench matrix metalloproteinases and inflammation,[38,39] and OFM is known to include a number of ECM proteins that have antibacterial properties in human tissue.[24] There are also additional ECM components that aid in neovascularization, which is critical for the effective delivery of protective immune components to the site of repair.[27]

The authors found the OFM graft and particulate easy to use and provided flexibility to augment the required surgical approach. For example, the OFM particulate enabled ready packing or filling of tunneled and undermined areas of the defects, and both products could be used with NPWT, as desired. The graft was found to be more robust compared to amnion-based grafts that may not be appropriate for these types of deep volumetric wounds of the lower extremity involving exposed structures. Compared to synthetic dermal matrices, OFM has a unique appearance in the wound bed as the dECM integrates. Partially degraded dECM components were typically visible on the surface of the newly formed vascularized tissue as the OFM integrated (eg, Fig. 4 C and D). This appears as a creamy golden-yellow substance and should not be mistaken for nonviable slough (or infection), and can, at the surgeon's discretion, be removed. In contrast, synthetic dermal matrices remain colored gray before cell infiltration and neovascularization.[34]

A comparable dECM technology that is used for inpatient soft-tissue reconstruction is porcine urinary bladder matrix (UBM). Urinary bladder matrix is supplied in a variety of sheet formulations in addition to a particulate. One distinguishing difference in how OFM and UBM behave clinically is the necessity for frequent repeated applications of UBM.[6,40,41] A noteworthy finding of this study was that the median number of OFM applications to achieve 100% granulation over exposed vital structure was one (a single) application. In comparison, synthetic dermal matrices may require repeated application because of graft loss or failure to integrate.[31,33,34,42,43]

Traditionally, the standard for soft-tissue reconstruction in large defects is accomplished by flap-based procedures. Although OFM grafts are not a replacement for these types of interventions, they offer an important alternative on the reconstructive ladder. Given the promising clinical outcomes in this retrospective, multicenter, real-world data set

of OFM graft and particulate use, these biological dECM options provide a viable solution for the successful management of complex lower-extremity soft-tissue reconstruction, even in contaminated wounds.

Limitations

This retrospective case series is not without its limitations that deserve further consideration. This was a single-arm retrospective case series that did not have a direct comparative arm. Considering that this was a multicenter study, there was no standardization regarding the secondary dressings used, follow-up timeline, or intraoperative techniques.

Conclusions

Ovine forestomach matrix graft and particulate are safe, cost-effective, and accessible treatment options, separately or in combined use, in volumetric lower-limb soft-tissue defects. When compared with similar dermal matrices, OFM graft and particulate may shorten the time to cover exposed vital structures and thereby decrease the overall time to attain definitive closure.

Acknowledgment: Aroa Biosurgery Limited for the preparation of this manuscript.
Financial Disclosure: This study was supported by Aroa Biosurgery Limited and Callaghan Innovation Limited (New Zealand) Growth Grant (MSMA1402).
Conflict of Interest: Brandon A. Bosque, DPM, and Shane G. Dowling, MSPAS, are employees of Aroa Biosurgery Limited; Barnaby C.H. May, PhD, is a shareholder of Aroa Biosurgery Limited, the company that manufactures the Myriad Matrix used in this study.

References

1. Frykberg RG, Attinger C, Smeets L, et al: Surgical strategies for prevention of amputation of the diabetic foot. J Clin Orthop Trauma **17:** 99, 2021.
2. Hakkarainen TW, Kopari NM, Pham TN, et al: Necrotizing soft tissue infections: review and current concepts in treatment, systems of care, and outcomes. Curr Probl Surg **51:** 344, 2014.
3. Flood MS, Weeks B, Anaeme KO, et al: Treatment of deep full-thickness wounds containing exposed muscle, tendon, and/or bone using a bioactive human skin allograft: a large cohort case series. Wounds **32:** 164, 2020.
4. Simman R, Hermans MHE: Managing wounds with exposed bone and tendon with an esterified hyaluronic acid matrix (eHAM): a literature review and personal experience. J Am Coll Clin Wound Spec **9:** 1, 2017.
5. Kozak GM, Hsu JY, Broach RB, et al: Comparative effectiveness analysis of complex lower extremity reconstruction: outcomes and costs for biologically based, local tissue rearrangement, and free flap reconstruction. Plast Reconstr Surg **145:** 608e, 2020.
6. Kraemer BA, Geiger SE, Deigni OA, et al: Management of open lower extremity wounds with concomitant fracture using a porcine urinary bladder matrix. Wounds **28:** 387, 2016.
7. Badylak SF: The extracellular matrix as a biologic scaffold material. Biomaterials **28:** 3587, 2007.
8. Kimmel H, Rahn M, Gilbert TW: The clinical effectiveness in wound healing with extracellular matrix derived from porcine urinary bladder matrix: a case series on severe chronic wounds. J Am Col Certif Wound Spec **2:** 55, 2010.
9. Bohn G, Liden B, Schultz G, et al: Ovine-based collagen matrix dressing: next-generation collagen dressing for wound care. Adv Wound Care (New Rochelle) **5:** 1, 2016.
10. Crapo PM, Gilbert TW, Badylak SF: An overview of tissue and whole organ decellularization processes. Biomaterials **32:** 3233, 2011.
11. Lun S, Irvine SM, Johnson KD, et al: A functional extracellular matrix biomaterial derived from ovine forestomach. Biomaterials **31:** 4517, 2010.
12. Bosque BA, Frampton C, Chaffin AE, et al: Retrospective real-world comparative effectiveness of ovine forestomach matrix and collagen/ORC in the treatment of diabetic foot ulcers. Int Wound J **19:** 741, 2022.
13. Lullove EJ: 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. Wounds **29:** 107, 2017.
14. Liden BA, May BCH: Clinical outcomes following the use of ovine forestomach matrix (endoform dermal template) to treat chronic wounds. Adv Skin Wound Care **26:** 164, 2013.
15. Raizman R, Hill R, Woo K: Prospective multicenter evaluation of an advanced extracellular matrix for wound management. Adv Skin Wound Care **33:** 437, 2020.
16. Chaffin AE, Buckley MC: Extracellular matrix graft for the surgical management of Hurley stage III hidradenitis suppurativa: a pilot case series. J Wound Care **29:** 624, 2020.
17. Chaffin AE, Dowling SG, Kosyk MS, et al: Surgical reconstruction of pilonidal sinus disease with concomitant extracellular matrix graft placement: a case series. J Wound Care **30** (suppl 7): S28, 2021.
18. Bohn GA, Chaffin AE: Extracellular matrix graft for reconstruction over exposed structures: a pilot case series. J Wound Care **29:** 742, 2020.
19. Desvigne MN, Bauer K, Holifield K, et al: Case report: surgical closure of chronic soft tissue defects using extracellular matrix graft augmented tissue flaps. Front Surg **7:** 559450, 2020.

20. DeNoto G, Ceppa EP, Pacella SJ, et al: A prospective, single arm, multi-center study evaluating the clinical outcomes of ventral hernias treated with OviTex 1S permanent reinforced tissue matrix: the BRAVO study 12-month analysis. J Clin Med **10:** 4998, 2021.
21. Sawyer M, Ferzoco S, DeNoto G III: A polymer-biologic hybrid hernia construct: review of data and early experiences. Polymers (Basel) **13:** 1928, 2021.
22. Ferzoco SJ: Early experience outcome of a reinforced bioscaffold in inguinal hernia repair: a case series. Int J Surg Open **12:** 9, 2018.
23. Parker MJ, Kim RC, Barrio M, et al: A novel biosynthetic scaffold mesh reinforcement affords the lowest hernia recurrence in the highest-risk patients. Surg Endosc **35:** 5173, 2020.
24. Dempsey SG, Miller CH, Hill RC, et al: Functional insights from the proteomic inventory of ovine forestomach matrix. J Proteome Res **18:** 1657, 2019.
25. Negron L, Lun S, May BCH: Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. Int Wound J **11:** 392, 2012.
26. Street M, Thambyah A, Dray M, et al: Augmentation with an ovine forestomach matrix scaffold improves histological outcomes of rotator cuff repair in a rat model. J Orthop Surg Res **10:** 165, 2015.
27. Irvine SM, Cayzer J, Todd EM, et al: Quantification of in vitro and in vivo angiogenesis stimulated by ovine forestomach matrix biomaterial. Biomaterials **32:** 6351, 2011.
28. Dempsey SG, Miller CH, Schueler J, et al: A novel chemotactic factor derived from the extracellular matrix protein decorin recruits mesenchymal stromal cells in vitro and in vivo. PLoS One **15:** e0235784, 2020.
29. Smith MJ, Dempsey SG, Veale RW, et al: Further structural characterization of ovine forestomach matrix and multi-layered extracellular matrix composites for soft tissue repair. J Biomater Appl **36:** 996, 2021.
30. Overbeck N, Nagvajara GM, Ferzoco S, et al: In-vivo evaluation of a reinforced ovine biologic: a comparative study to available hernia mesh repair materials. Hernia **24:** 1293, 2020.
31. Li H, Lim P, Stanley E, et al: Experience with NovoSorb Biodegradable Temporising Matrix in reconstruction of complex wounds. ANZ J Surg **91:** 1744, 2021.
32. Yao M, Attalla K, Ren Y, et al: Ease of use, safety, and efficacy of integra bilayer wound matrix in the treatment of diabetic foot ulcers in an outpatient clinical setting: a prospective pilot study. JAPMA **103:** 274, 2013.
33. Iorio ML, Goldstein J, Adams M, et al: Functional limb salvage in the diabetic patient: the use of a collagen bilayer matrix and risk factors for amputation. Plast Reconstr Surg **127:** 260, 2011.
34. Solanki NS, York B, Gao Y, et al: A consecutive case series of defects reconstructed using NovoSorb Biodegradable Temporising Matrix: initial experience and early results. J Plast Reconstr Aesthet Surg **73:** 1845, 2020.
35. Gonzalez SR, Wolter KG, Yuen JC: Infectious complications associated with the use of Integra: a systematic review of the literature. Plast Reconstr Surg Glob Open **8:** e2869, 2020.
36. Rodriguez Collazo ER, Rathbone CR, Barnes BR: A retrospective look at integrating a novel regenerative medicine approach in plastic limb reconstruction. Plast Reconstr Surg Glob Open **5:** e1214, 2017.
37. Geiger SE, Deigni OA, Watson JT, et al: Management of open distal lower extremity wounds with exposed tendons using porcine urinary bladder matrix. Wounds **28:** 306, 2016.
38. Sarikaya A, Record R, Wu CC, et al: Antimicrobial activity associated with extracellular matrices. Tissue Eng **8:** 63, 2002.
39. Brennan EP, Reing J, Chew D, et al: Antibacterial activity within degradation products of biological scaffolds composed of extracellular matrix. Tissue Eng **12:** 2949, 2006.
40. Valerio IL, Campbell P, Sabino J, et al: The use of urinary bladder matrix in the treatment of trauma and combat casualty wound care. Regen Med **10:** 611, 2015.
41. Parry JA, Shannon SF, Strage KE, et al: Urinary bladder matrix grafting: a simple and effective alternative to flap coverage for wounds in high-risk orthopaedic trauma patients. J Orthop Trauma **36:** e152, 2021.
42. Wagstaff MJ, Schmitt BJ, Caplash Y, et al: Free flap donor site reconstruction: a prospective case series using an optimized polyurethane biodegradable temporizing matrix. Eplasty **15:** e27, 2015.
43. Shakir S, Messa CA IV, Broach RB, et al: Indications and limitations of bilayer wound matrix-based lower extremity reconstruction: a multidisciplinary case-control study of 191 wounds. Plast Reconstr Surg **145:** 813, 2020.

Case Report

Soft Tissue Reconstruction With Ovine Forestomach Matrix After Wide Excision of Plantar Fibromatosis

Abby B Duplechain, BS[1]; Brandon A Bosque, DPM[2]; Caleb W Fligor, MD[1]; Abigail E Chaffin, MD[1]

Abstract

Background. Plantar fibromatosis, or Ledderhose disease, presents as plantar fascia nodules caused by hyperactive proliferating fibroblasts. These benign tumorous growths can persist causing pain as well as reduced mobility and quality of life. Plantar fibromatosis may not respond to conservative nonsurgical treatment resulting in surgical intervention, including wide excision of the affected tissue and subsequent reconstruction. Reconstruction of the full-thickness plantar defect is challenging given the location, and recurrence rates are relatively high. Here we present a staged reconstruction of plantar fibromatosis following wide excision using a biologic graft to regenerate the neodermis and subsequent skin grafting. This reconstructive approach provided an alternative to free flap transfer, with excellent functional outcomes.

ePlasty 2023;23:e20. Epub March 2023

Key words: plantar fibromatosis; ovine forestomach matrix; extracellular matrix; Ledderhose disease

Introduction

Plantar fibromatosis (PF; Ledderhose disease) is a rare hyperproliferative benign lesion of the plantar aponeurosis.[1] Lesions are characterized by the proliferation of highly differentiated fibroblasts, abnormal collagen deposition, and multinucleated giant cells.[2,3] While originating at the aponeurosis, severe disease may invade the underlying musculature or overlying subcutaneous tissue, dermis, and epidermis.[4] In the early phases of the disease, symptom-oriented therapies such as offloading orthotic inserts, oral anti-inflammatory medications, corticosteroid injections, and physical therapy can be offered. In some jurisdictions radiotherapy is offered and has been shown to reduce pain.[5] Although these therapies may improve a patient's symptoms, they do not prevent disease progression.[6] Where persistent symptomatic nodes have developed, surgical options may be considered for excision of the lesion(s).

Local surgical excision of lesions typically suffers from poor outcomes with a recurrence rate ranging from 57% to 100%.[1] Wide excision (2-3–cm margin) may slightly reduce these recurrence rates (8%-80%).[1] When the fibroma invades the underlying and/or overlying structures, excision with the fibroma may be required, making primary closure challenging or impossible. In these scenarios, large-volume defects with exposed vital structures (eg, tendon, bone, neurovasculature) have traditionally been managed with free-flap reconstruction. In addition to the technical difficulty and donor site morbidity, free-flap reconstruction to the plantar foot offers unique challenges because it is a weight-bearing surface.[7]

Here we present a case report of a 60-year-old male patient with a history of recurrent PF, which was refractory to conservative management and 3 previous local excisions. Rather than a wide excision and free-flap reconstruction, the full-thickness defect was reconstructed using a staged reconstruction with application of an ovine forestomach matrix (OFM) graft, regeneration of the plantar neodermis, and closure via a split-thickness skin graft.

Materials and Methods

The procedure was performed under general anesthesia involving plastic surgery and orthopedic surgery teams. The orthopedic surgeon performed wide excision of the lesion, involving the plantar fascia and superficial flexor muscles **(Figure 1B)**. The excision created a defect measuring approximately 15 x 8 x 1.5 cm. The defect was full thickness, with exposure of vital structures including approximately 8 cm of flexor tendon and exposure of periosteum of the first metatarsal phalangeal joint. The resected tissue underwent pathology review with immunohistochemistry

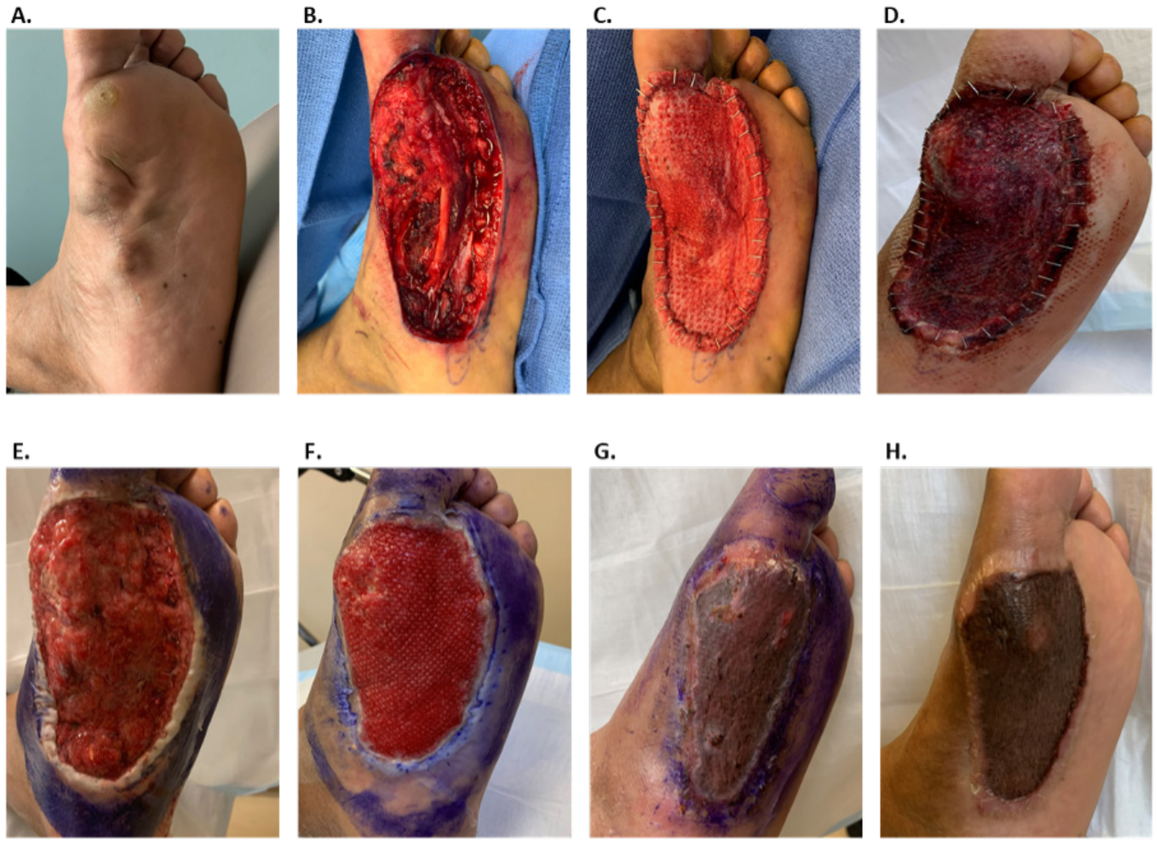


FIGURE 1. A) A 60-year-old male with recurrent plantar fibromatosis to the left foot; B) Full-thickness wide excision; C) OFM graft placement; D) postoperative day 4; E) postoperative day 10, thin coverage of first metatarsal phalangeal joint noted; F) postoperative day 33; G) postoperative day 67, 14 days post STSG; H) postoperative day 138, 3 months post STSG.

staining. Spindle cells were positive for ß-catenin and smooth muscle actin (SMA), while negative for cytokeratin (AE1/AE3), S100, and desmin. These pathology findings are compatible with a diagnosis of deep plantar fibromatosis.[8]

Immediately following the initial wide excision, an OFM graft (Myriad Matrix, 3-layer, Aroa Biosurgery Limited) was placed over the full-thickness defect. The graft was trimmed and fixed using absorbable sutures and staples **(Figure 1C)**. A non-adherent dressing was applied, with negative pressure wound therapy (NPWT; 125 mmHg) being used as the secondary dressing. During the immediate postoperative period, the patient was strictly offloaded (knee scooter and immobilizing ankle boot), with guidance against any ambulation or pressure application. The patient underwent weekly dressing changes in the outpatient wound center. At postoperative day 10 **(Figure 1E)** there was an area of thin soft tissue coverage over the first metatarsal phalangeal joint, and the patient was treated with additional weekly outpatient applications of OFM (Endoform Natural, Aroa Biosurgery Limited) to promote targeted neodermis formation over this area. NPWT dressings were changed twice weekly and non–weight-bearing status was maintained for 4 weeks. At postoperative day 53 a split-thickness skin graft (STSG; 0.0018 inches) was performed, a non-adherent dressing and NPWT (125 mmHg) were applied, and non–weight-bearing precautions were continued. The patient was followed for approximately 9 months.

Results

The patient with a >10-year history of recurrent PF **(Figure 1A)** presented for definitive treatment with wide local excision of the recurrent lesions and immediate coverage of the full-thickness defect using an OFM graft. The goal of placing the OFM graft was to provide tissue coverage over the exposed vital structures as part of a staged reconstruction as an alternative to a free flap procedure. At postoperative day 4 the OFM graft was well adhered and beginning to integrate **(Figure 1D)**, and by day 19 it was fully integrated except for a small area over the first metatarsal phalangeal joint. Due to the limited coverage at this site, placement of a STSG was delayed until postoperative day 53 and the defect was healed by day 75 **(Figure 1G)**, 14 days after the STSG was performed. At long-term follow-up (postoperative day 138, **Figure 1H**) the defect remained healed and functional tissue persisted. At approximately 9 months, the patient had excellent range of motion, with pliable conforming dermal tissues over the site (see supplementary Video). The patient was referred to an orthotist for customized offloading orthotic inserts that can be worn with normal footwear. The patient was educated regarding lifelong foot checks and appropriate footwear to minimize surgical-site breakdown. At 9 months the patient reported normal pain-free walking and the resumption of an active lifestyle after >10 years of PF.

Discussion

PF has been reported to account for 18.9% of all soft tissue tumors affecting the foot and ankle.[9] Where conservative interventions fail, surgical intervention is often considered as a last resort to restore function. The challenge with surgical intervention is restoration of the plantar surface post excision. These full-thickness defects may be healed via secondary intention,[10] delayed application of a STSG,[11] or free tissue transfer. While popular, free-flap reconstruction may lead to insensate tissue, donor site morbidity, or flap necrosis due to it being a weight-bearing surface. Additionally, revision surgeries may be required to de-bulk the flap and achieve a functional foot profile.

As an alternative to a free-flap reconstruction we considered a staged approach using a biologic graft, and to our knowledge this is the first report of a staged reconstruction using a biologic graft after wide excision of PF. The OFM graft is a decellularized extracellular matrix developed for applications in soft tissue regeneration,[12] including staged reconstructions of full-thickness defects with exposed structures.[13] OFM provides a scaffold to support host cell infiltration, adhesion, and migration, as well as the formation of new local vascular networks.[14]

Although products such as the OFM graft do not supersede or replace flap-based reconstructions, these devices represent an alternative option where free or rotational flaps are not appropriate or possible due to anatomy, patient selection, potential for donor site morbidity, or surgical training. Further, free flaps can potentially increase the cost of care as they require several hours of operating room time, additional operating room resources, anesthesia, cost to manage the donor site, and possibly longer length of stay to monitor the flap viability. This case represents a successful reconstruction of a large plantar weight-bearing foot using an OFM graft and weekly visits in the outpatient center. With this approach, soft tissue coverage and contour restoration were achieved as a less invasive and technically demanding alternative to a free-flap reconstruction. Additionally, this approach avoided the creation of a bulky flap that could have reduced ambulation, made footwear challenging, and led to an insensate plantar surface. The described approach of conservative staged surgical management of PF may offer patients a new option for consideration.

Conclusions

In conclusion, this case report highlights the utility of an OFM graft as part of a wide excision and staged reconstruction of PF as an alternative to a free-flap reconstruction.

References

1. Young JR, Sternbach S, Willinger M, Hutchinson ID, Rosenbaum AJ. The etiology, evaluation, and management of plantar fibromatosis. *Orthop Res Rev.* 2019;11:1-7. doi:10.2147/ORR.S154289
2. de Palma L, Santucci A, Gigante A, Di Giulio A, Carloni S. Plantar fibromatosis: an immunohistochemical and ultrastructural study. *Foot Ankle Int.* Apr 1999;20(4):253-7. doi:10.1177/107110079902000408
3. Evans HL. Multinucleated giant cells in plantar fibromatosis. *Am J Surg Pathol.* Feb 2002;26(2):244-8. doi:10.1097/00000478-200202000-00012
4. van der Veer WM, Hamburg SM, de Gast A, Niessen FB. Recurrence of plantar fibromatosis after plantar fasciectomy: single-center long-term results. *Plast Reconstr Surg.* Aug 2008;122(2):486-491. doi:10.1097/PRS.0b013e31817d61ab
5. de Haan A, van Nes JGH, Werker PMN, Langendijk JA, Steenbakkers R. Radiotherapy for patients with Ledderhose disease: Long-term effects, side effects and patient-rated outcome. *Radiother Oncol.* Mar 2022;168:83-88. doi:10.1016/j.radonc.2022.01.031
6. Veith NT, Tschernig T, Histing T, Madry H. Plantar fibromatosis--topical review. *Foot Ankle Int.* Dec 2013;34(12):1742-6. doi:10.1177/1071100713505535
7. Li X, Cui J, Maharjan S, Lu L, Gong X. Reconstruction of the foot and ankle using pedicled or free flaps: Perioperative flap survival analysis. *PLoS One.* 2016;11(12):e0167827. doi:10.1371/journal.pone.0167827
8. Lacka DE, Nasierowska-Guttmejer A. Fibromatosis - immunohistochemical evaluation, differential diagnosis from gastrointestinal tumors, and other mesenchymal tumours. *Prz Gastroenterol.* 2019;14(1):79-85. doi:10.5114/pg.2019.83429
9. Tay AYW, Tay KS, Thever Y, Hao Y, Yeo NEM. An epidemiological review of 623 foot and ankle soft tissue tumours and pseudo-tumours. *Foot Ankle Surg.* Jun 2021;27(4):400-404. doi:10.1016/j.fas.2020.05.004
10. Ocampo-Garza J, Azevedo Cunha R, Silva Pereira C, et al. Plantar fibromatosis: Surgical approach of a giant bilateral case. *Int J Dermatol.* Mar 2018;57(3):365-367. doi:10.1111/ijd.13840
11. Wapner KL, Ververeli PA, Moore JH, Jr, Hecht PJ, Becker CE, Lackman RD. Plantar fibromatosis: a review of primary and recurrent surgical treatment. *Foot Ankle Int.* Sep 1995;16(9):548-51. doi:10.1177/107110079501600906
12. Lun S, Irvine SM, Johnson KD, et al. A functional extracellular matrix biomaterial derived from ovine forestomach. *Biomaterials.* Jun 2010;31(16):4517-29. doi:10.1016/j.biomaterials.2010.02.025
13. Bohn GA, Chaffin AE. Extracellular matrix graft for reconstruction over exposed structures: a pilot case series. *J Wound Care.* Dec 2 2020;29(12):742-749. doi:10.12968/jowc.2020.29.12.742
14. Irvine SM, Cayzer J, Todd EM, et al. Quantification of in vitro and in vivo angiogenesis stimulated by ovine forestomach matrix biomaterial. *Biomaterials.* Sep 2011;32(27):6351-61. doi:l10.1016/j.biomaterials.2011.05.040

Affiliations: [1]Division of Plastic Surgery, Department of Surgery, Tulane University School of Medicine, New Orleans, LA; [2]Aroa Biosurgery Limited, Auckland, New Zealand

Correspondence: Abigail E Chaffin, MD; achaffin@tulane.edu

Ethics: Written informed consent was obtained from the patient for the publication of this report.

Funding: This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures: BAB is employee of Aroa Biosurgery Limited (Auckland, New Zealand). AEC is consultant of Aroa Biosurgery Limited.

ISSN: 2469-5777

Taarea et al. Trauma Cases Rev 2024, 10:102
DOI: 10.23937/2469-5777/1510102
Volume 10 | Issue 1
Open Access

Trauma Cases and Reviews

CASE SERIES

Early Experience with Ovine Forestomach Matrix for the Reconstruction of Abdominal Defects following Emergency Open Abdomen Surgery at a Level 2 Trauma Center

Roberto Taarea, DO, Abigail Florence, MD, Blake Bendixen, MD and Christine A Castater, MD*

Department of Trauma and Acute Care Surgery, WellStar Kennestone Hospital, Marietta, GA, USA

***Corresponding author:** *Christine A Castater, MD, MBA, Department of Surgery, Morehouse School of Medicine, Atlanta, 80 Jesse Hill Hr Dr SE #2c-144 Atlanta, GA 30303 USA, Tel: 404-616-1417, Fax: 404-616-1417*

Abstract

Background: Abdominal defects resulting from emergency open abdominal (OA) procedures require complex treatment algorithms and continue to burden both patients and healthcare providers due to increased risk of morbidity and complications. When primary closure of the abdominal subcutaneous and dermal tissues cannot be achieved, negative pressure wound therapy (NPWT) is among the most common treatment options. While biologic hernia meshes are often deployed to reinforce the abdominal wall or bridge fascia, the use of biologic grafts to specifically aid granular infill of abdominal defects is less reported.

Methods: This retrospective, observational case series (n = 3 abdominal defects) presents the authors' initial experience using a biological graft, ovine forestomach matrix (OFM), with and without NPWT to aid tissue infill of abdominal defects post OA surgery. De-identified data was collated via the electronic medical record and results reported herein.

Results: The mean time to 100% graft integration was 19.3 ± 0.9 days with a mean overall healing time of 9 ± 2 weeks, with no complications to a mean follow-up of 50 ± 14 weeks. Concomitant NPWT usage, with weekly NPWT dressing changes had a mean healing time of 3.7 ± 0.9 weeks.

Conclusion: These initial findings demonstrated that OFM graft especially when used concomitantly with NPWT is safe and may decrease the overall time to healing of complex abdominal defects resulting from emergency OA surgery.

Keywords

Extracellular matrix, Ovine forestomach matrix, Soft tissue trauma, Open abdomen, Volumetric tissue loss, Laparotomy

Abbreviations

OA: Open Abdomen; NPWT: Negative Pressure Wound Therapy; OFM: Ovine Forestomach Matrix; STSG: Split-Thickness Skin Graft; WTD: Wet-to-Dry; MLL: Morel Lavallee Lesion

Introduction

Although open abdomen (OA) is a often used for "damage control" of catastrophic intra-abdominal injuries, it is typically associated with high complications rates and poor outcomes [1,2]. Closure of the OA typically proceeds with primary closure of the abdominal wall fascia that may be reinforced with a synthetic or biological surgical mesh. Ideally, the abdominal subcutaneous and dermal tissues are primarily closed but a large number of patients have either insufficient or contaminated tissue and are therefore left with significant soft tissue defects requiring delayed repair and/or regeneration. These abdominal defects are often defined by large and irregular wound beds. While there are a variety of pedicled and free flap reconstruction techniques available, these approaches are surgically complex with high donor site morbidity, so they are rarely indicated after damage control surgery [3]. Currently, NPWT is a mainstay to promote granulation tissue and expedite wound healing in abdominal defects [4]. NPWT can provide coverage to exposed viscera, protect the site from bacterial contamination, and manage wound

Citation: Taarea R, Florence A, Bendixen B, Castater CA (2024) Early Experience with Ovine Forestomach Matrix for the Reconstruction of Abdominal Defects following Emergency Open Abdomen Surgery at a Level 2 Trauma Center. Trauma Cases Rev 10:102. doi.org/10.23937/2469-5777/1510102

Accepted: February 08, 2024: **Published:** February 10, 2024

exudate all while stimulating formation of granulation tissue [5]. Abdominal wounds managed with NPWT may ultimately be closed via a split thickness skin graft (STSG), or by secondary intention following standard wound care. Management of abdominal defects with NPWT has consistently led to improved wound closure rates compared to standard wound care methods such as wet-to-dry (WTD) or other standard daily dressing changes [6]. Despite these advantages, NPWT duration and management still places a significant burden on patients and health care teams. In order to achieve improved and increased abdominal wound healing, Seidel, et al. [7] reported an average NPWT treatment duration of 14.6 ± 9.1 days. In a retrospective review of 37 full thickness abdominal wounds, DeFranzo, et al. [8] reported an average NPWT treatment duration of 18 days (range; 11-25 days). These studies prove that it is valuable to both patients and the healthcare system to continue to explore strategies that reduce the duration of NPWT management of abdominal wounds. Reduced healing time not only leads to reduced costs of care but also improves patients' quality of life [9-11]. Biologic meshes were originally used for hernia and OA surgery with contaminated fields, but have largely been replaced by a synthetic mesh or by choosing to forego the use of a mesh largely due to suboptimal clinical outcomes and cost of biologic meshes [12,13]. In these cases, it is necessary to consider how to facilitate expedited subcutaneous tissue healing with the plan of a delayed and definitive closure technique. Cutaneous tissue regeneration using mammalian tissue derived biologic grafts are now an established part of the reconstructive ladder [14,15]. The use of these biologic grafts extends to a variety of complex and often contaminated wounds, including abdominal wounds [16,17]. In complex wound reconstruction, biologic grafts are often used concomitantly with NPWT, and studies have shown that concomitant use can shorten the overall healing time [9-11,18]. Biologic meshes were originally used for hernia and OA surgery with contaminated fields, but have largely been replaced by a synthetic mesh or by choosing to forego the use of a mesh largely due to suboptimal clinical outcomes and cost of biologic meshes [12,13]. In these cases, it is necessary to consider how to facilitate expedited subcutaneous tissue healing with the plan of a delayed and definitive closure technique. Cutaneous tissue regeneration using mammalian tissue derived biologic grafts are now an established part of the reconstructive ladder [14,15]. The use of these biologic grafts extends to a variety of complex and often contaminated wounds, including abdominal wounds [16,17]. In complex wound reconstruction, biologic grafts are often used concomitantly with NPWT, and studies have shown that concomitant use can shorten the overall healing time [18].

Ovine forestomach matrix based biologic grafts are now routinely utilized in soft tissue regeneration across a range of contaminated defects including hidradenitis suppurativa [19], pilonidal sinus [20], chronic lower extremity defects [21,22] and necrotizing soft tissue infections [23]. In the search for new cost-effective options to improve healing of contaminated traumatic wounds the authors has begun to use OFM-based biologic grafts in combination with NPWT across a range of complex soft tissue defects. In this case report, we examine our initial experience using OFM-based grafts in conjunction with NPWT to treat complex abdominal defects resulting from emergency OA surgery.

Methods

The case report included three consecutive patients (n = 3) that had undergone reconstruction of abdominal defects resulting from OA surgery using OFM-based grafts during the period November 2021 to June 2022 at a single facility. OFM in either graft (Myriad Matrix Soft Tissue Bioscaffold™, Aroa Biosurgery Limited, Auckland, New Zealand) or morselized ('particulate' or 'powder') format (Myriad Morcells™, Aroa Biosurgery Limited, Auckland, New Zealand) were used in accordance with the manufacturer's instructions for use. Patients were given general anesthesia, the surgical site prepared with povidone-iodine (Betadine®, Cumulus Pharmaceutical LLC, and Cheyenne, WY, USA) and the patient surgically draped. The abdominal defects were thoroughly debrided to remove all necrotic tissue and lavaged with sterile saline. Defect dimensions and depth were recorded with a surgical ruler post-debridement. Utilization of either the OFM graft (3- or 5-layer), morselized OFM, or a combination of the two products was based on clinical judgement of the attending surgeon. The OFM devices were rehydrated (< 5 mins, sterile saline), trimmed to size as required and fixed to the defect edges or subcutaneous tissues in instances of undermined tissue with either suture or staples. The defects were subsequently dressed with a non-adherent petroleum-based contact layer (Xeroform®, McKesson Medical-Surgical, Irving, TX, USA), then NPWT interface black foam, and NPWT system (V.A.C.®, 3M/KCI, St. Paul, MN, USA). NPWT systems were set to 125 mmHg, and dressings changed every 5-7 days. At the discretion of the surgical team, definitive closure of each defect was achieved via STSG or secondary intention, according to institutional protocols.

Results

Case 1

A 49-Year-old male with morbid obesity, bipolar disorder, and history of drug use presented after a high-velocity motor vehicle accident with acute hypotension, ruptured liver and bladder requiring two damage-control laparotomies. Fascia was closed three days following a second exploratory laparotomy with the subcutaneous tissue remaining open. Five days after fascial closure, the patient was undergoing dressing change and the

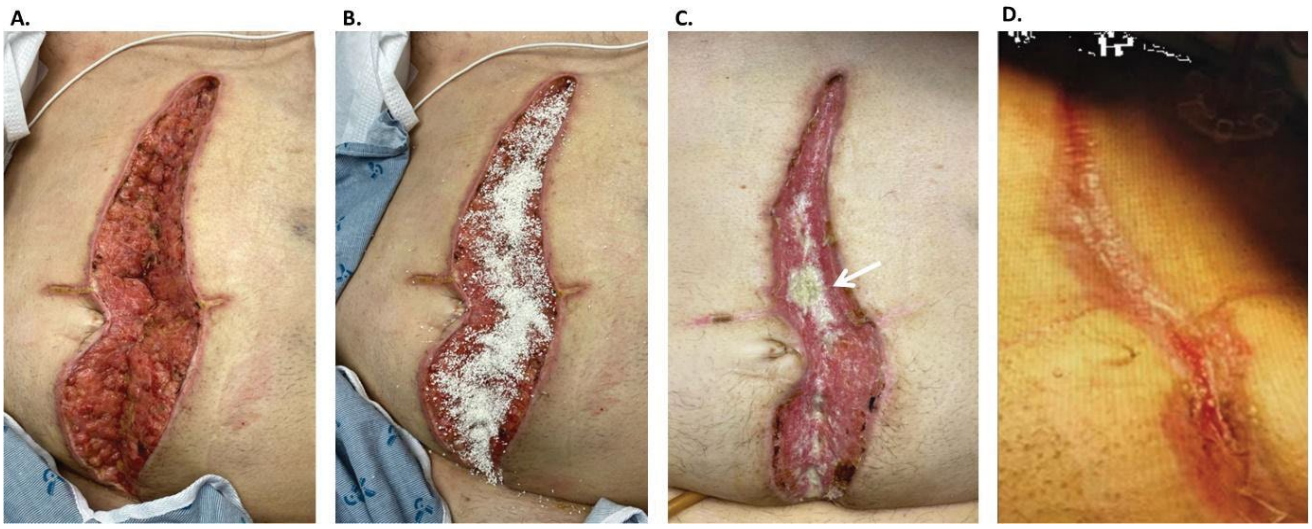


Figure 1: Case 1, open abdominal defect following MVA and multiple damage-control laparotomies: (a) Intra-operative, post debridement; (b) OFM particulate applied to the bed of the OA defect, prior to rehydration; (c) Week 3. Infill of the defect and graft integration. A small area of residual graft (white arrow) was present; (d) Week 6. Closure via secondary intention.

fascial closure was found to have partially dehisced (Figure 1a), and the decision was made to apply OFM particulate at the bedside in the ICU due to the patient's poor medical state. Prior to application of the OFM, the defect was irrigated with Betadine® solution and saline. Post debridement the defect involving the subcutaneous and cutaneous tissues measured ~31 cm × 7 cm × 4 cm (Figure 1a). A single application of morselized OFM (1000 mg) was applied to the base of the defect and rehydrated *in situ* with sterile saline and blood (Figure 1b). The defect was dressed with a petroleum-based contact layer and standard NPWT (125 mmHg) was placed. NPWT was used for 2 weeks, with weekly dressing changes. Complete integration of the OFM was achieved in 21 days, with the regenerated tissue being flush to the level of adjacent skin (Figure 1c). Definitive closure was achieved by secondary intention at 6 weeks resulting in functional soft tissue with satisfactory contour restoration and no complications (Figure 1d). The patient subsequently underwent planned ventral hernia repair at 20 weeks. Abdominal cutaneous tissues previously regenerated with OFM were sufficiently robust to allow for primary closure following hernia repair and healing was uneventful and without complication. No recurrence was noted at last follow-up (70 weeks).

Case 2

A 67-Year-old female with morbid obesity, history of stroke, and dementia presented after a motor vehicle accident requiring an initial exploratory laparotomy with findings of multiple mesenteric lacerations and ischemic bowel. The abdomen was left open, and then closed to the level of the fascia two days later following a right hemicolectomy and small bowel resection. NPWT was placed to manage the defect involving the sub-cutaneous tissues. Three days later a subsequent open procedure was undertaken to further resect small bowel, perform a colo-enteric anastomosis, and loop ileostomy, with closure to the level of the fascia and NPWT (Figure 2a). To follow, the patient required four serial washouts and debridement of subcutaneous tissue due to lack of improvement and areas of tissue necrosis. The patient continued to be managed with NPWT. After 17 days without improvement, OFM particulate (500 mg) and graft (5-layer, 10 × 20 cm) were placed in the defect (~16 cm × 8 cm × 6 cm) involving the subcutaneous tissues (not shown). Prior to graft placement the defect was irrigated with Betadine® solution and saline, then the graft rehydrated (saline), trimmed as needed and secured with absorbable suture. The graft was further bolstered to the underlying defect with NPWT (125 mmHg). Ten days later, a large Morel-Lavallee lesion (MLL) of the right abdomen was noted, likely from the seatbelt at the time of trauma. This large volumetric abdominal defect ultimately communicated with the previous midline defect. The MLL was opened via a transverse incision (Figure 2b), and OFM placed to address the MLL (~20 × 10 × 6 cm). OFM particulate (500 mg) was first placed in the base and tunneled areas of the MLL and rehydrated with exudate. OFM graft (5-layer, 10 × 20 cm) was then placed on top the particulate hydrated with saline, and semi-implanted with partial closure. The entire defect was dressed with NPWT (125 mmHg). Three days later, the MLL was further explored, debrided and extended transversely (Figure 2c). OFM particulate (1500 mg) and graft (5-layer, 10 × 20 cm) were placed as previously described, and a partial closure of the MLL was achieved. The entire defect was dressed with a petroleum contact layer dressing and standard NPWT (125 mmHg), maintained for 4 weeks, with weekly dressing changes. Nineteen days following the third OFM application the wound bed had granulated and at week 5 the transverse MLL

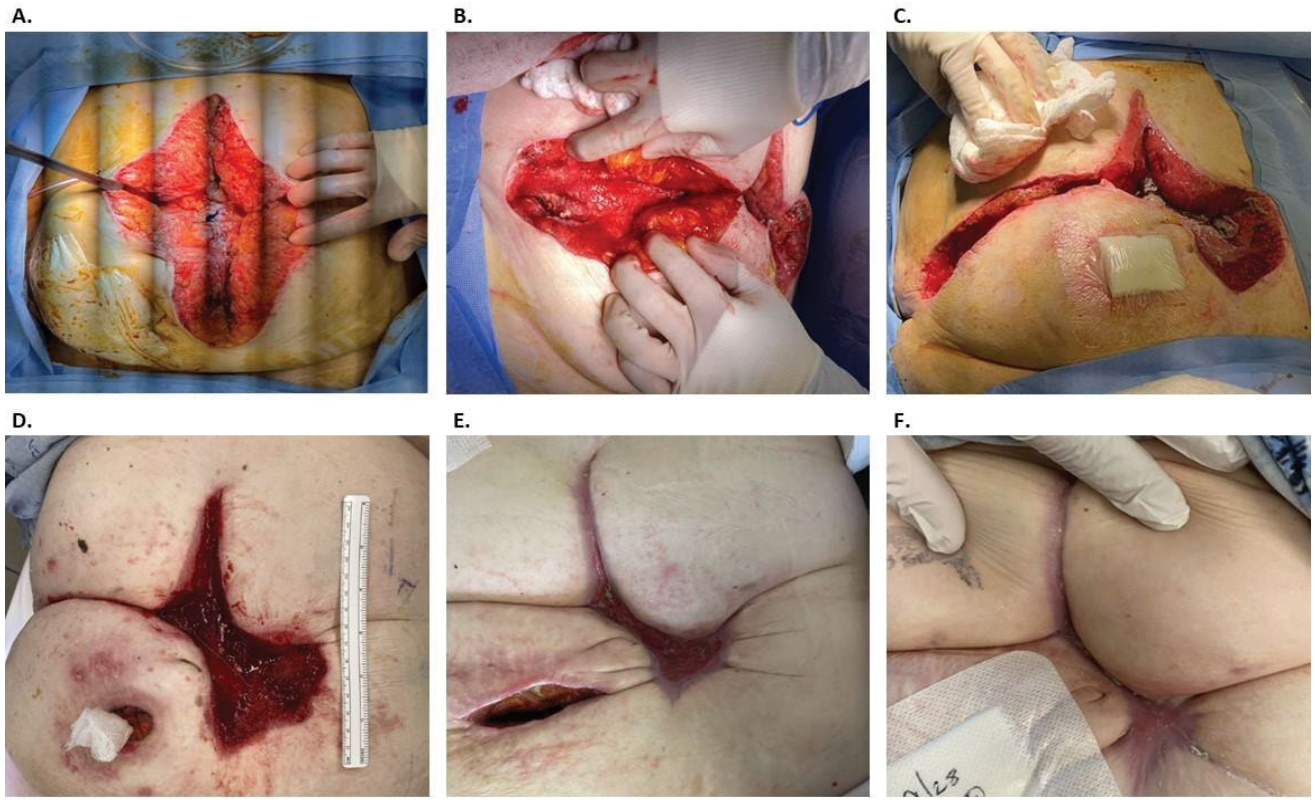


Figure 2: Case 2: (a) Open abdominal defect following multiple laparotomies and closure to the level of the fascia; (b) Exploration of the MLL transverse to the original mid-line defect, and prior to OFM graft placement; (c) Further exploration of the MLL defect and prior to the second OFM graft application; (d) Week 5 eradication of the transverse MLL defect; (e) Week 7; (f) Week 13.

defect of the right side had been eradicated (Figure 2d), and the original midline defect was filled with granulation tissue to the height of the surrounding skin. Definitive epithelialization was achieved by secondary intention at 13 weeks resulting in functional soft tissue coverage with satisfactory contour restoration and no major complications (Figure 2e and Figure 2f). Of note, a small area of dehiscence was noted, but subsequently healed with outpatient local wound care in 3 weeks. No recurrence was noted at last follow-up (23 weeks).

Case 3

A 51-Year-old male presented after high-velocity motor vehicle accident requiring multiple damage-control laparotomies to repair the diaphragm and bladder, as well as for a small bowel resection. The OA was initially closed at the level of the fascia and managed with NPWT. The patient had a small area of fascial dehiscence seven days after closure (Figure 3a). The decision was made to proceed with repair of the sub-cutaneous and dermal tissues, until the abdominal wall could be closed via a delayed planned ventral hernia repair. The defect was irrigated with Betadine® solution and saline, prior to sharp debridement resulting in a defect measuring 24 cm × 4 cm × 2 cm (Figure 3a). OFM particulate (1000 mg) was applied directly to the defect (Figure 3b). OFM graft (10 × 20 cm, 3-layer) was placed to cover the entire defect (Figure 3c) and into the undermined areas and was secured with synthetic absorbable sutures. The defect was dressed with a petroleum-based contact layer dressing and standard NPWT (125 mmHg). NPWT was used for 5 weeks, with weekly dressing changes (Figure 3d). Complete integration of the OFM device was achieved by day 18. Definitive epithelialization was achieved by STSG applied at week 7, with 100% stake of the STSG at one week. Long term follow-up at 16 weeks showed the defect was restored with functional tissue coverage, until planned ventral hernia repair could be completed (Figure 3e). There were no complications or recurrence at last follow-up (57 weeks). The patient ultimately underwent a planned ventral hernia repair at 41 weeks following re-epithelialization and was uneventful and without complications.

Discussion

OA commonly occurs after damage-control of catastrophic intra-abdominal injuries, but the long-term management and outcome potential of these defects continues to be a challenge in trauma and emergency general surgery. Many strategies have evolved to close the fascia including vacuum-assisted closure, mesh-mediated fascial traction, dynamic wound closure system and fascial bridging [24]. Fascial defects after OA surgery occur either as the result of dehiscence after primary closure or from a lack of tissue to achieve

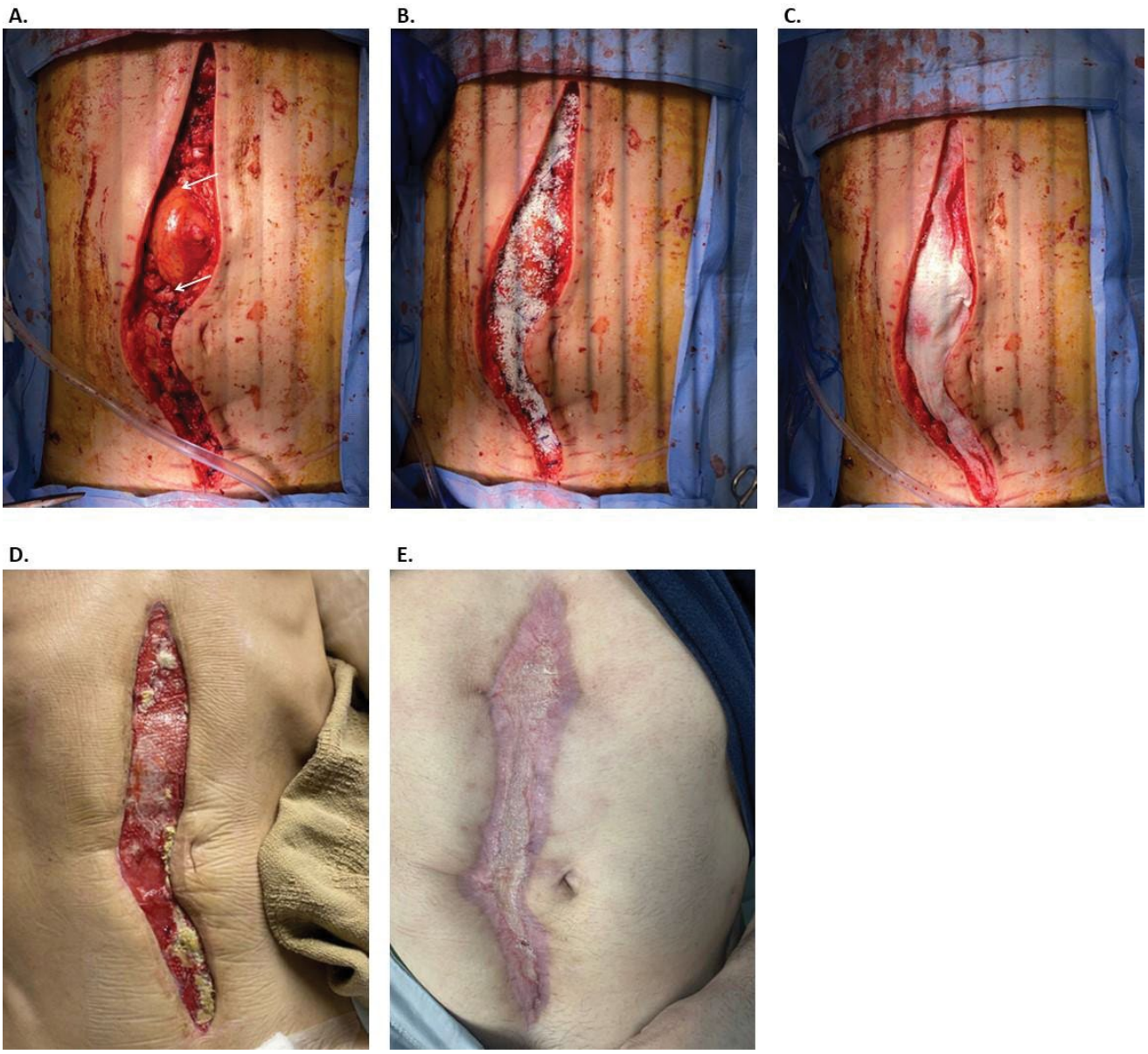


Figure 3: Case 3, Open abdomen due to multiple damage-control laparotomies: (a) Intra-operative post debridement. Prior primary closure to the level of the fascia had dehisced leaving a small area of exposed viscera (indicated between the two white arrows); (b) Application of OFM particulate (1000 mg); (c) Application of OFM graft (10 × 20 cm, 3-layer); (d) Week 5; (e) Long term follow-up at 16 weeks, 9 weeks post application of a STSG.

primary closure. The resultant abdominal defect presents a challenge to the surgical team as do all large volumetric wounds involving potentially contaminated and inflamed soft tissues. Granulating the abdominal defect is the primary focus to enable either coverage by secondary intention or by placement of a split thickness skin graft. NPWT has been used extensively to encourage the formation of well vascularized tissue over these abdominal defects. Often NPWT is used in conjunction with various surgical meshes which can be placed to reinforce or bridge the fascial defect. Many studies have been presented in the literature describing this approach [25,26], however complete healing of the abdominal defects have been reported to take 6 months or more [27]. The use of biologic grafts to aid regeneration of abdominal cutaneous tissues doesn't replace the need for surgical meshes to reinforce the abdominal wall post OA surgery. Rather the intent of biologic grafts, overlaid on the fascia and/or subcutaneous tissues is to aid formation of robust granulation tissue to cover the abdominal defect. Many of these defects will require complex abdominal wall reconstruction techniques in the future for definitive fascial closure. There are very few reports in the literature describing the application of biologic grafts to accelerate vascularized tissue formation within abdominal defects, prior to definitive closure. Puckett, et al. [16] described healing of abdominal defects with the biologic graft, urinary bladder matrix. In their retrospective case series, the authors described initial fascial closure with a dynamic wound closure system, and then once fascial closure was achieved, powdered biologic graft and sheet were applied to the primary myofascial closure and subcutaneous tissue. Abdominal

defects were then covered with NPWT, with a reported healing rate of approximately 8 weeks across 50 patients. Single case reports have been published using porcine dermal graft after abdominal wall dehiscence [17] and fish-skin graft in a partial thickness abdominal dehiscence [28].

In this retrospective case series, we present the successful treatment of three consecutive abdominal defects resulting from OA defects where OFM grafts were used to regenerate well vascularized granulation tissue. In these instances, the fascial tissue had already been primarily closed. In all three cases, the defects were at or beyond the level of the fascia, clean-contaminated (Grade 2) and in one case, there was exposed viscera due to partial dehiscence (Case 3). The mean time to complete integration of the graft was 19.3 ± 0.9 days. One patient received a split thickness skin graft at week 7 and the mean time to compete healing across all three cases was 9 ± 2 weeks, with no complications to a mean follow-up of 50 ± 14 weeks. Case 1 and 3 required only a single application of the OFM graft. Case 2 received three separate applications of the OFM grafts, not due to graft failure or lack of incorporation but due to extension of the initial defect after revealing the interconnected MLL.

There is some controversy in the literature as to the true effectiveness of NPWT in the management of OA defects and the ability to facilitate faster time to closure, but regardless, there are noteworthy increases in cost when utilizing NPWT [29]. It is postulated that by using a biological graft to expediate tissue regeneration providers can potentially reduce the number of dressing changes and overall duration of NPWT, thereby reducing financial burden for patients and facilities alike [30]. The use of biologic grafts adjunctively with NPWT to synergistically improve wound healing trajectory has been widely described in the scientific literature [31-33], and shorten the duration of NPWT use [34]. Across our current cases the concurrent NPWT usage ranged from 2-5 weeks with a mean of 3.7 ± 0.9 weeks. We note that our current approach to concomitant NPWT utilization with OFM grafts adhered to NPWT dressing change frequency of 5-7 days, whereas other published protocols report a dressing change frequency of up to 2 days using a porcine urinary bladder matrix graft [16].

Abdominal defects resulting from OA surgery are often contaminated [35]. The success of OFM in reconstructions involving contaminated fields, such as abdominal defects, may be attributable to its ability to form well-vascularized tissue [36] while concurrently modulating wound proteases that are known to prolong inflammation [37]. This, in theory, should allow the patient's native immune system to primarily fend off microbial contamination thereby minimizing clinical infection and ultimately facilitating progression of the defect to definitive closure [38].

This study is comprised of observations from a single center with all the other limitations of a retrospective case series such as small sample size and no comparative cohort group. While the results of this case series are promising, there is a need for future research to expand the number of patients to validate these initial results. Future studies may involve a controlled prospective study design with an aim to compare the overall healing rates, complications, including herniation and fascial dehiscence, and NPWT utilization when used in combination with OFM grafts.

Conclusions

This case series builds on a growing body of evidence that OFM can be utilized to facilitate the formation of robust, well-vascularized soft tissue in large contaminated volumetric soft tissue defects and reduce complications. The OFM grafts were shown to complement existing NPWT protocols and may reduce the frequency of dressing changes associated with NPWT usage in abdominal soft tissue defects.

Acknowledgement

The authors wish to acknowledge Aroa Biosurgery Limited for editorial assistance in preparing this manuscript. We thank the efforts of the nurses and surgical team of WellStar Kennestone Hospital.

Sources of Support

No funding was provided for this study. RT is a consultant for Aroa Biosurgery Limited.

Statement of Author Contribution

All authors contributed significantly and equally to the direct patient care, collation of retrospective data, data analysis, and development of the manuscript.

References

1. Cristaudo A, Jennings S, Gunnarsson R, DeCosta A (2017) Complications and mortality associated with temporary abdominal closure techniques: A systematic review and meta-analysis. Am Surg 83: 191-216.
2. Regner JL, Kobayashi L, Coimbra R (2012) Surgical strategies for management of the open abdomen. World J Surg 36: 497-510.
3. Sacks JM, Broyles JM, Baumann DP (2012) Flap coverage of anterior abdominal wall defects. Semin Plast Surg 26: 36-39.
4. Stevens P (2009) Vacuum-assisted closure of laparostomy wounds: A critical review of the literature. Int Wound J 6: 259-266.
5. Hutan M, Bartko C, Majesky I, Prochotsky A, Sekac J, et al. (2014) Reconstruction option of abdominal wounds with large tissue defects. BMC Surg 8: 50.
6. Seidel D, Diedrich S, Herrle F, Thielemann H, Marusch F, et al. (2020) Negative pressure wound therapy vs conventional wound treatment in subcutaneous abdominal wound healing impairment: The SAWHI randomized clinical trial. JAMA Surg 155: 469-478.

7. Seidel D, Lefering R (2022) NPWT resource use compared with conventional wound treatment in subcutaneous abdominal wounds with healing impairment after surgery: SAWHI randomized clinical trial results. Ann Surg 275: e290-e298.
8. DeFranzo AJ, Pitzer K, Molnar JA, Marks MW, Chang MC, et al. (2008) Vacuum-assisted closure for defects of the abdominal wall. Plast Reconstr Surg 121: 832-839.
9. Giordano S, Garvey PB, Baumann DP, Liu J, Butler CE (2017) Primary fascial closure with biologic mesh reinforcement results in lesser complication and recurrence rates than bridged biologic mesh repair for abdominal wall reconstruction: A propensity score analysis. Surgery 161: 499-508.
10. Shao JM, Ayuso SA, Deerenberg EB, Elhage SA, Prasad T, et al. (2022) Biologic mesh is non-inferior to synthetic mesh in CDC class 1 & 2 open abdominal wall reconstruction. Am J Surg 223: 375-379.
11. Katzen M, Ayuso SA, Sacco J, Ku D, Scarola GT, et al. (2023) Outcomes of biologic versus synthetic mesh in CDC class 3 and 4 open abdominal wall reconstruction Surg Endosc 37: 3073-3083.
12. Wilson RB, Farooque Y (2022) Risks and prevention of surgical site infection after hernia mesh repair and the predictive utility of ACS-NSQIP. J Gastrointest Surg 26: 950-964.
13. Sandvall BK, Suver DW, Said HK, Mathes DW, Neligan PC, et al. (2016) Comparison of synthetic and biologic mesh in ventral hernia repair using components separation technique. Ann Plast Surg 76: 674-679.
14. Valerio IL, Sabino JM, Dearth CL (2016) Plastic surgery challenges in war wounded II: Regenerative medicine. Adv Wound Care 5: 412-419.
15. Erba P, Ogawa R, Vyas R, Orgill DP (2010) The reconstructive matrix: A new paradigm in reconstructive plastic surgery. Plast Reconstr Surg 126: 492-498.
16. Puckett Y, Caballero B, McReynolds S, Richmond R, Ronaghan C (2019) Successful closure of the open abdomen utilizing novel technique of dynamic closure system with biologic xenograft. International Journal of Abdominal Wall and Hernia Surgery 4.
17. Bounovas A, Antoniou GA, Laftsidis P, Bounovas A, Antoniou SA, et al. (2008) Management of abdominal wound dehiscence with porcine dermal collagen implant: Report of a case. Ostomy Wound Manage 54: 44-48.
18. Mari W, Younes S, Naqvi J, Issa AA, Oroszi TL, et al. (2019) Use of a natural porcine extracellular matrix with negative pressure wound therapy hastens the healing rate in stage 4 pressure ulcers. Wounds 31: 117-122.
19. Chaffin AE, Buckley MC (2020) Extracellular matrix graft for the surgical management of hurley stage III hidradenitis suppurativa: A pilot case series. J Wound Care 29: 624-630.
20. Chaffin AE, Dowling SG, Kosyk MS, Bosque BA (2021) Surgical reconstruction of pilonidal sinus disease with concomitant extracellular matrix graft placement: A case series. J Wound Care 30: S28-S34.
21. Bosque BA, Frampton C, Chaffin AE, Bohn GA, Woo K, et al. (2022) Retrospective real-world comparative effectiveness of ovine forestomach matrix and collagen/ORC in the treatment of diabetic foot ulcers. Int Wound J 19: 741-753.
22. Bosque BA, Dowling SG, May BCH, Kaufman R, Zilberman I, et al. (2023) Ovine forestomach matrix in the surgical management of complex lower-extremity soft-tissue defects. J Am Podiatr Med Assoc 113: 22-81.
23. Cormican MT, Creel NJ, Bosque BA, Dowling G, Rideout PP, et al. (2023) Ovine forestomach matrix in the surgical management of complex volumetric soft tissue defects: A retrospective pilot case series. Index ePlasty 23: e66.
24. Huang Q, Li J, Lau WY (2016) Techniques for abdominal wall closure after damage control laparotomy: From temporary abdominal closure to early/delayed fascial closure-a review. Gastroenterol Res Pract 2016: 2073260.
25. Caviggioli F, Klinger FM, Lisa A, Maione L, Forcellini D, et al. (2014) Matching biological mesh and negative pressure wound therapy in reconstructing an open abdomen defect. Case Rep Med 2014: 235930.
26. Ginting N, Tremblay L, Kortbeek JB (2010) Surgisis® in the management of the complex abdominal wall in trauma: A case series and review of the literature. Injury 41: 970-973.
27. Lee EI, Chike-Obi CJ, Gonzalez P, Garza R, Leong M, et al. (2009) Abdominal wall repair using human acellular dermal matrix: A follow-up study. Am J Surg 198: 650-657.
28. Di Mitri M, Di Carmine A, Thomas E, Iacobacci G, Collautti E, et al. (2023) Fish skin graft: Narrative review and first application for abdominal wall dehiscence in children. Plast Reconstr Surg Glob Open 11: e5244.
29. Cirocchi R, Birindelli A, Biffl WL, Mutafchiyski V, Popivanov G, et al. (2016) What is the effectiveness of the negative pressure wound therapy (NPWT) in patients treated with open abdomen technique? A systematic review and meta-analysis. J Trauma Acute Care Surg 81: 575-584.
30. Sasse K, Ackerman E, Brandt J (2013) Complex wounds treated with matristem xenograft material: Case series and cost analysis. Medicine.
31. Fleming ME, O'Daniel A, Bharmal H, Valerio I (2014) Application of the orthoplastic reconstructive ladder to preserve lower extremity amputation length. Ann Plast Surg 73: 183-189.
32. Dillingham CS, Jorizzo J (2019) Managing ulcers associated with pyoderma gangrenosum with a urinary bladder matrix and negative-pressure wound therapy. Adv Skin Wound Care 32: 70-76.
33. Gabriel A, Gollin G (2006) Management of complicated gastroschisis with porcine small intestinal submucosa and negative pressure wound therapy. J Pediatr Surg 41: 1836-1840.
34. Sreelesh LS, Bhandari PL (2017) An easy technique for negative-pressure wound therapy for extremities using collagen powder and sterile gloves. Indian J Surg 79: 81-83.
35. Li PY, Yang D, Liu D, Sun SJ, Zhang LY (2017) Reducing surgical site infection with negative-pressure wound therapy after open abdominal surgery: A prospective randomized controlled study. Scand J Surg 106: 189-195.
36. Overbeck N, Nagvajara GM, Ferzoco S, May BCH, Beierschmitt A, et al. (2020) In-vivo evaluation of a reinforced ovine biologic: A comparative study to available hernia mesh repair materials. Hernia 24: 1293-1306.
37. Negron L, Lun S, May BCH (2012) Ovine forestomach matrix biomaterial is a broad spectrum inhibitor of matrix metalloproteinases and neutrophil elastase. Int Wound J 11: 392-397.
38. Zhao R, Liang H, Clarke E, Jackson C, Xue M, et al. (2016) Inflammation in chronic wounds. Int J Mol Sci 17: 2085.