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Dehydrated amniotic membrane allografts for the treatment of chronic wounds: a case series

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Dehydrated amniotic membrane allografts for the treatment of chronic wounds: a case series

A retrospective case series demonstrating the use of dehydrated human amniotic membrane (dHAM) allografts in the treatment of wounds of various aetiologies. Amniotic membrane was applied to a series of chronic wounds referred to a formal wound clinic for aggressive management, after prior, traditional treatment methods were found ineffective, over a period of 1 month. In each case, failure of traditional therapy was followed by placement of a dehydrated amniotic membrane allograft and the healing time course was documented with charted measurements. Wounds treated with the amniotic membrane allograft demonstrated improved healing, with a change in the healing trajectory from that previously noted. Dehydrated human amniotic membrane represents a potentially effective addition to existing wound care therapies, with further formal clinical studies indicated.

amniotic membrane; chronic wounds; allograft

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Declaration of interest: Dr Fetterolf is Chief Medical Officer of MiMedx Group, Inc. which manufactures the EpiFix product used in this paper. Dr Forbes is currently employed in a wound clinic, but has no financial interest in the material presented.

Both the primary cause and the underlying aetiology of wound persistence can be numerous and diverse. Primary pathological conditions underlying chronic wounds include diabetic neurovascular ulcers, chronic venous insufficiency, microvascular arterial disease, post-traumatic wounds and postoperative wound dehiscence. The underlying aetiologies for the development of chronicity can involve a number of mechanisms, including underlying infection, vascular insufficiency, unbalanced wound healing biomolecular microenvironments, and other factors.[1]

Recognition of the specific conditions and underlying predisposing factors for chronicity have led to the recent creation of comprehensive, evidence-based guidelines for wound care, as well as formal wound centres.[2,3] The development of evidence-based guidelines has improved the general approach to care of non-healing wounds, and has made new information available to the larger clinician population.[3–11]

Multidisciplinary algorithms for addressing chronic wounds have been advanced and are available from a number of sources.[2,3,12–14] Basic principles of care for chronic wounds of most types employ a number of steps, including:

- Sharp debridement and removal of non-vital tissue
- Maintenance of a moist wound healing environment
- Avoidance of cytotoxic therapies, such as povidone-iodine or silver agents
- Assessment and correction of macro- and microvascular disease
- Aggressive treatment of infection
- Physical offloading of pressure sites, including bespoke footwear and full-contact casting.

These wound therapy approaches were standardised in the Diversified Clinical Services, Inc. wound clinic, as part of its comprehensive, standard operating procedures.[15]

Despite careful attention using these methods, wounds may still remain open and not close after a month or more of therapy. Indeed, even wounds that meet typical surrogate healing endpoints may still fail without close observation and reassessment on a regular basis.[16] 'Failure' is typically defined as the

The authors wish to thank MiMedx Group, Inc. for providing the samples used in the treatment of these patients.

inability of a wound to heal by at least 50%, after being treated for a period of 1 month,[16,17] a definition used by Medicare (US national social insurance programme) to define an endpoint needed to permit a move to more expensive biological therapies.

The relatively recent development of synthetic skin substitutes, natural allografts and xenografts has presented new hope in clinicians' efforts to close refractory ulcers. The general issues with rising medical costs have been of particular interest, given the economic significance of non-healing wounds in the patient populations under consideration.[18–22]

Human amniotic membrane has been described in peer-reviewed literature as a wound care treatment for over 100 years. Davis reported a series of 550 cases using skin transplantation, as early as 1910.[23] John conducted a review of the use of amniotic membrane in wounds, treating ulcers, burns and other dermal injuries, as well as applications in plastic and reconstructive surgery at other sites.[24] The widespread use of the material, however, was limited due to a variety of obvious logistic problems, including inconsistent presentation of material, difficulty processing placentas into amniotic membrane treatments, and difficulty in handling and surgical use, sterilisation, transportation, and storage.[3,8,25,26]

Over the past several years, a dehydrated version of human amniotic membrane has been prepared and developed for use as a wound therapy. Currently used for over 6 years in eye surgery, some 45 000 cases have occurred using the material for pterygium repair, burns and conjunctival reconstruction surgery, even in children (internal product information, MiMedx Group, Inc.). From an analysis of both manufacturer's information and the medical literature, there are virtually no significant medical complications or side effects reported from the use of the material.[27]

In particular, the use of dehydrated human amniotic membrane has been explored as a cost-effective approach to facilitating chronic wound closure in our practice, and we believe the material could be competitive with alternative strategies in both price and outcome.[28] In preliminary case studies, similar to those described here, the material seemed to work quickly to improve cost to closure, and it is comparably priced to competing biological products. The material does not require special handling or storage precautions. It is pliable at room temperature, and has a shelf life of up to 5 years. In its current commercial configuration, it comes in a number of sizes, which permits the use of smaller pieces as a wound heals if multiple pieces are required, reducing waste. Finally, because fewer applications are necessary, this reduces total treatment costs to the patient, including the total amount of copay and deductible amounts patients must pay.

This clinical series was undertaken to document the use and effectiveness of dehydrated human amniotic membrane (dHAM) allografts as a viable biologic treatment in non-healing wounds. Used historically on many wound types in the natural form, as noted above, human amniotic membrane has gained wide use in ophthalmic wounds and surgery. The material was used here to confirm the applicability of dHAM in cutaneous wounds as well.

Methods

A retrospective series of five representative patients were selected from a larger group of 12 patients presenting to an advanced state-of-the-art wound clinic (Diversified Clinical Services, Inc.), between May and September 2011. Patients treated had received dehydrated human amniotic membrane allografts after failing initial traditional therapies using conservative algorithms.[15]

Adult patients, over 18 years old, with non-healing wounds were offered the commercially available dHAM allograft (EpiFix; MiMedx Group, Inc.), after failing to heal by at least 50% after at least 1 month of traditional therapy.

Participating chronic wound patients were selected from those receiving the allografts, who were representative of a diverse range of underlying aetiologies to demonstrate the applicability and effectiveness of dHAM allografts. Initial therapy of all patients included traditional care using evidence-based protocols of the Diversified Clinical Services group,[15] and documented failure of traditional therapy after 1 month of usual care, using the criteria stated above.

The retrospective patient selection ultimately resulted in patients being treated with the following underlying pathologies:

- Venous leg ulcers
- Crush injury
- Arterial insufficiency
- Immunologic skin disease/scleroderma
- Snake bite.

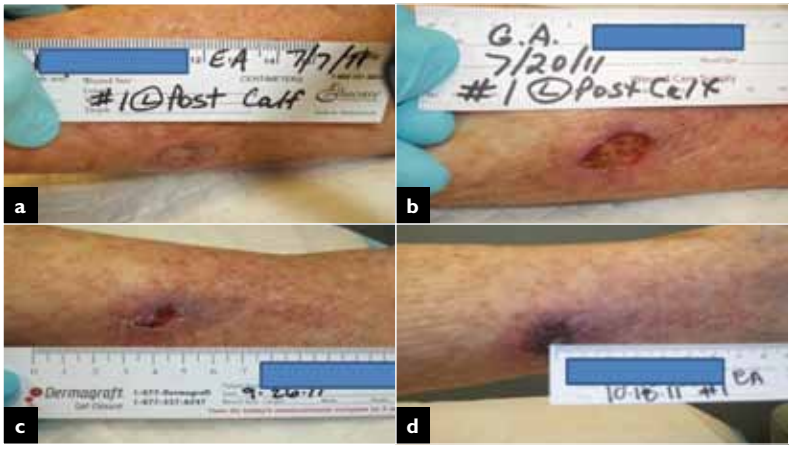

Fig 1. Case 1 photo series. Venous leg ulcer documented at clinic admission, (a), and at the placement of grafts, (b, c). Final photo shows resolved wound with good epithelialisation, (c)

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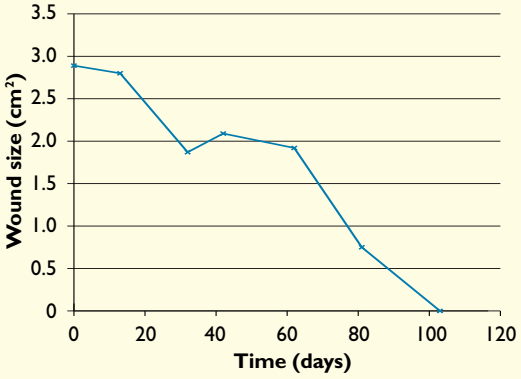
Fig 2. Chronological improvement in wound size over time in patient 1



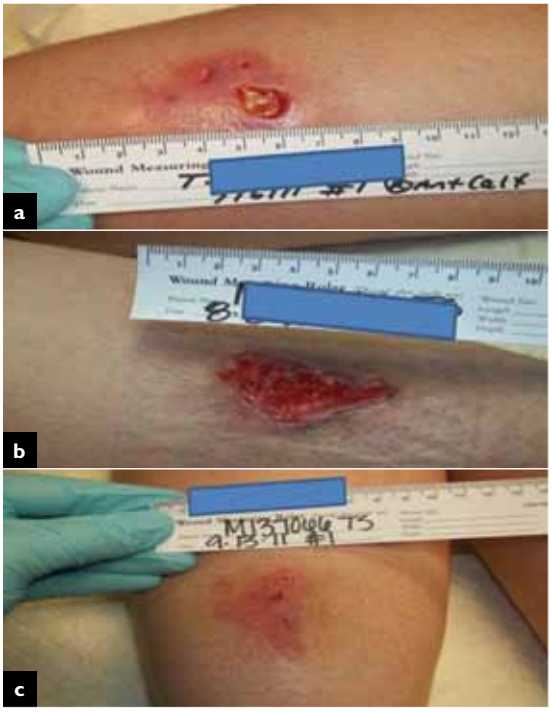


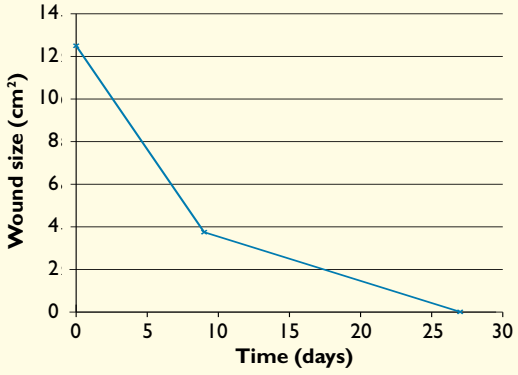
Fig 3. Case 2 photo series. Crush injury documented at clinic admission, (a), at the point of graft placement, (b), and at the time of the last visit, (c)

All patients had appropriately signed release forms, as standard procedure, as part of their treatment in the wound clinic.

The dHAM allografts were applied according to the manufacturer's specifications and approach.[15] The wound bed was prepared using sharp debridement, to provide a viable wound base prior to graft implantation and the wound was examined to be free from clinical signs of infection.

Graft selection was undertaken to fit an appropriate-sized graft and minimise waste of the material. The graft was cut using sterile dry scissors to fit within the wound margin or provide minimal onlay overlap. Graft orientation, with epithelial layer facing up, was confirmed by noting the embossed lettering on the material.

Fig 4. Chronological improvement in wound size over time in patient 2



The primary dressing included a non-adherent contact layer created by a commercially available non-adherent dressing (either Adaptic Touch [Systagenix] or Mepital [Mölnlycke]) and was not disturbed for at least 2 weeks. A secondary dressing, using a moist saline gauze dressing, was applied to provide a moist wound healing environment.

Other support therapies were permitted including offloading, compression, and decompression therapies. Patients were typically treated with only one graft, with the option of an additional graft at the clinician's prerogative.

All patients were followed-up in clinic by the investigating clinician (JF), typically on a weekly basis. At each follow-up visit, the wound was photographed and direct measurements of the wound area were taken (length×width). The primary endpoint was wound closure, defined as full epithelialisation of the wound, assessed both clinically and as documented in the photographs.

Results

- **Patient 1** was a 97-year-old white female, who presented with venous leg ulcer of >1 month's duration, involving her left calf. The patient had some history of hypertension, though this was not considered significant. The patient had experienced no improvement of her underlying lesion after several debridements, aggressive compression and oral antibiotics (trim sulfa). Dehydrated human amniotic membrane was applied in two applications, over a 3-month period, with significant improvement observed in wound closure (Fig 1). Time to healing from graft placement to wound epithelialisation was 91 days (Fig 2).
- **Patient 2** was a 31-year-old, otherwise healthy, white female who sustained a crush injury to her left calf and developed a chronic wound (Fig 3). The patient developed seroma necrosis that required inpatient surgical debridement. After surgery, patient

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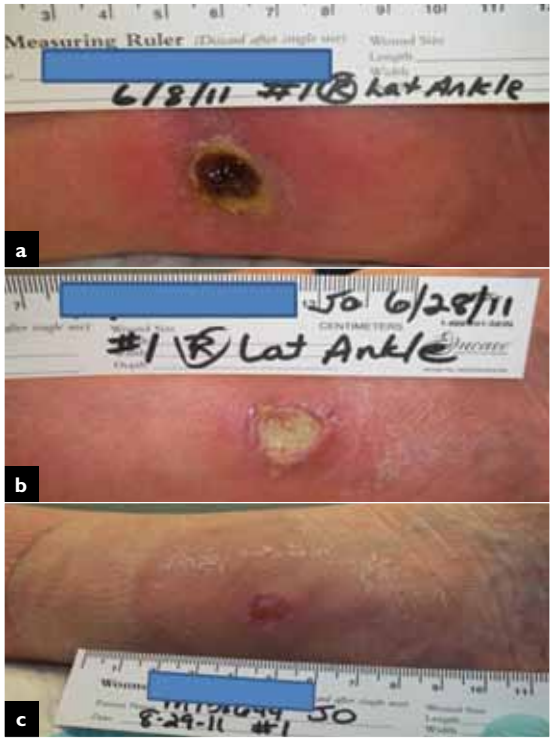
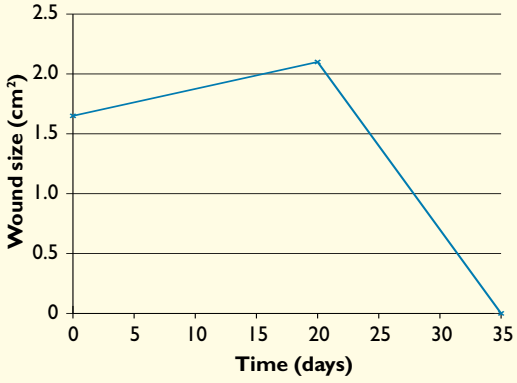


Fig 5. Case 3 case series. Chronic arterial insufficiency documented at clinic admission, (a), at the point of graft placement, (b), and at the time of the last visit, (c)

Fig 6. Chronological improvement in wound size over time in patient 3



developed a 2+ pitting lymphoedema below the knee, successfully treated with serial multilayer compression wraps (Profore; Smith & Nephew). At the time of EpiFix application, oedema was well controlled and managed with a two-layer compression stocking (Tubigrip; Mölnlycke) at 20mm/Hg. dHAM was applied after surgery and the patient healed completely with significant epithelialisation and minimal scarring. Time to healing from graft placement to wound epithelialisation was 39 days (Fig 4).

• **Patient 3** was a 60-year-old, nonsmoking white male with chronic arterial insufficiency of the right ankle, of 3 weeks' duration on presentation. The patient's wound initially showed no improvement after revascularisation surgery (Fig 5). The patient

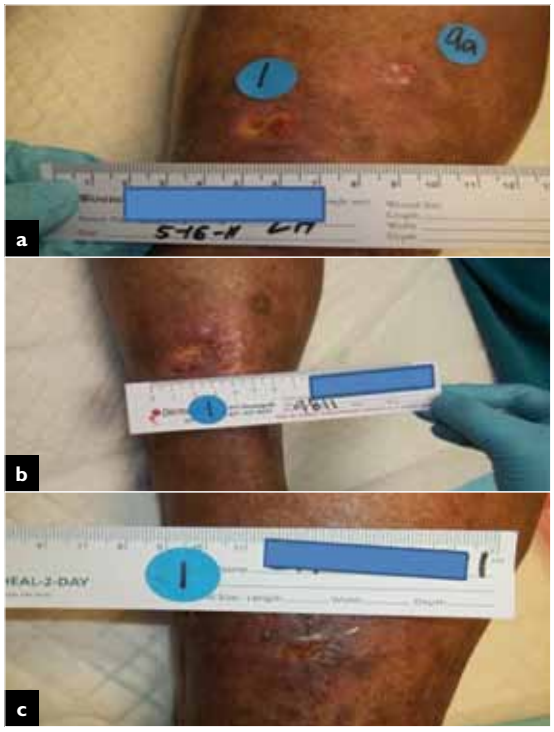


Fig 7. Case 4 photo series. Scleroderma and venous leg ulcers documented at clinic admission, (a), at the point of graft placement, (b), and at the time of the last visit, (c)

was treated with dHAM therapy and the wound closed within 1 month of application, leaving no scar tissue behind. Time to healing from graft placement to wound epithelialisation was 16 days (Fig 6).

• **Patient 4** was a 56-year-old black female with scleroderma and venous leg ulcers who had not responded to therapy, including aggressive debridement, antibiotics and dressing changes over a 4-year period (Fig 7). Therapy also included oral and topical anti-inflammatories (prednisone dosepak, kenalog cream 0.01%). Of two initial wounds, one was noted to be healed completely within 1 month, after one application of dHAM. The second wound showed 30% improvement over a 1-month period. Time to healing from graft placement to wound epithelialisation was 154 days (Fig 8).

• **Patient 5** was a 49-year-old white female, who sustained a snake bite and pit viper envenomation to the left posterior heel, with subsequent development of cellulitis requiring hospitalisation, intravenous antibiotics (vancomycin IV), dressing changes (Biostep Ag; Smith & Nephew), surgical sharp debridement and oral antibiotics (Bactrim DS). After 4 weeks of unsuccessful use of traditional methods, dHAM was applied to the wound area. The site was noted to heal within 2 weeks of initial application (Fig 9). Of interest, there was essentially no improvement in depth of the wound, and

Fig 8. Chronological improvement in wound size over time in patient 4

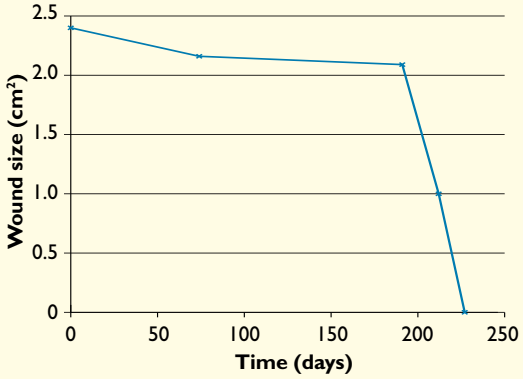
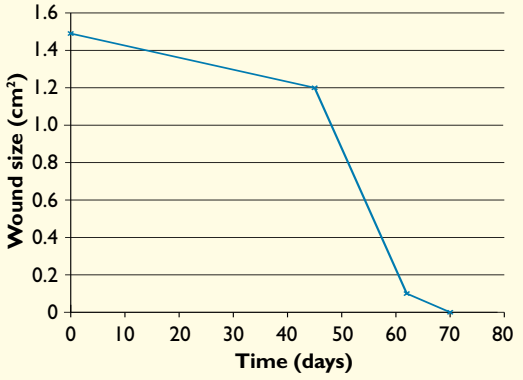


Fig 10. Chronological improvement in wound size over time in patient 5



even some regression with the development of necrotic subcutaneous tissue requiring debridement, following standard protocol, prior to the application of the allograft. Time to healing from graft placement to wound epithelialisation was 26 days (Fig 10).

Discussion

The recent development of a stabilised form of dHAM, through proprietary processing methods, has resulted in a clinical wound allograft that has demonstrated effectiveness in healing wounds, burns and reconstructive surgery in the eye.

Each of the cases discussed were presented to a formal wound clinic for care and were found to have a non-healing wound. Patient history and physical findings suggested that these wounds would not further respond to standard conservative measures and would benefit from a more advanced biological therapy. Patients were treated with debridement, application of dHAM, according to manufacturer's recommendations, and followed to completion. No adverse effects were noted, in keeping with the historically noted safety of the allografts.

Human amniotic membrane exhibits a number of unique properties, including:

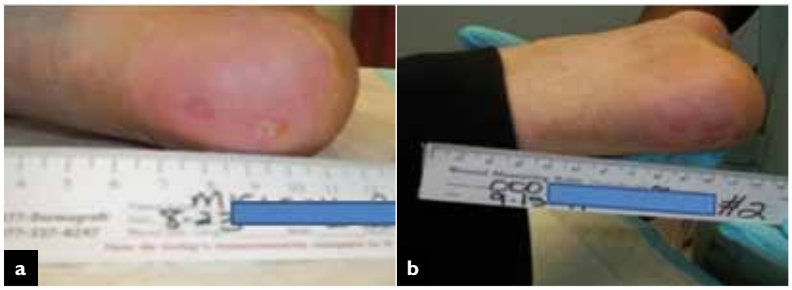


Fig 9. Case 5 photo series. Snake bite wound documented at clinic admission, (a), at the point of graft placement, and at the time of the last visit, (b)

- Provides a matrix for cellular migration and proliferation[29]
- Promotes increased healing through a variety of processes[30]
- Is non-immunogenic, lacking human leukocyte antigen (HLA) tissue antigens, but also including anti-immunogenic cytokines[31,32]
- Presents a natural biologic barrier to external contaminants
- Contains essential growth factors, including PDGF alpha, PDGF beta, TGF alpha, TGF beta, VEGF, and others
- Reduces inflammation[33]
- Reduces scar tissue formation[34]
- Has unique inherent antibacterial properties[35,36]
- Is capable of reducing pain at the treatment site.[37,38]

Each of the patients in this case series were representative examples of the type of referrals to a chronic wound clinic. Each was treated with dehydrated human amniotic membrane after failure of traditional methods and advanced therapies.

Conclusion

This study presents a series of cases for whom traditional wound therapy treatment was unsuccessful and where treatment with advanced biologic grafts was recommended. Recently expanded to include the treatment of other wounds, amniotic membrane shows promise in treating chronic wounds unresponsive to traditional therapies even within a formal wound clinic environment directed by evidence-based treatment algorithm guidelines.

Patients treated responded over several weeks from application where a non-healing wound was observed. As an advanced biologic therapy, application of an amniotic membrane allograft is not indicated for the routine treatment of wounds. Similar to other advanced biologic treatments, it is indicated for those wounds that demonstrate a pattern of resolution that indicates where a non-healing wound environment is present. Further investigation with this material in formal clinical trials is clearly warranted to confirm the cost-effective nature of this therapy. ■

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