Treatment of bacterially contaminated lower extremity ulcers with a fatty acid-containing wound matrix: a case series

Objective: The aim was to evaluate the effectiveness of a marine omega fatty acid-containing multimodal wound matrix (MWM) in reducing bacterial contamination and supporting wound area reduction (WAR) in patients with hard-to-heal wounds of varying aetiologies.
Method: A prospective, single-site, pilot case series of patients with hard-to-heal wounds. All wounds were considered non-healing prior to inclusion as they had failed to achieve at least 50% WAR after at least four weeks of standard of care (SoC) treatments. Patients were seen once weekly for wound assessments, matrix application and dressing changes. Baseline and weekly fluorescence images, standard wound images and wound measurements were obtained.
Results: A total of three patients, two with venous leg ulcers (VLUs) and one with a diabetic foot ulcer (DFU) were enrolled in this pilot study. The mean baseline wound age prior to study enrolment was 24 weeks, with a mean baseline wound size of 8.61cm^2. The two VLUs went on to complete closure. The DFU displayed a total WAR of 53% by six weeks, when the patient was lost to follow-up due to a geographical relocation. The mean percentage area reduction of all wounds combined was 82% upon study completion.
Conclusion: The use of MWM proved to be effective and safe in this patient cohort. The wounds included in this case series failed to enter a healing trajectory with SoC wound therapies. The MWM supported wound closure and reduced bacterial loads in this patient cohort.
Declaration of interest: No funding was provided for this case series. The MWM to be studied was provided by the sponsor (OCM; Omeza, US). The author has no conflicts of interest to declare.

antimicrobial ● DFU ● diabetic foot ulcer ● fatty acids ● hard-to-heal wound ● VLU ● venous leg ulcer ● wound ● wound care ● wound dressing ● wound healing ● wound matrix

Hard-to-heal wounds attract an estimated annual Medicare spend of $28.1–96.8 billion USD.[1–3] The longer a wound remains unhealed, the more costs accumulate, as does the risk for downstream complications such as infection and amputation.[4,5] It is well-accepted that wound repair is a complex process that involves multiple interlinking phases for regeneration of healthy tissue to occur. The healing cascade is an intricate process, with platelets, neutrophils, macrophages, endothelial cells, keratinocytes and fibroblasts all playing an important part. A delay or stall in wound area reduction (WAR) and healing is often due to a variety of systemic and local factors, primary among these are a disorganised extracellular matrix (ECM), excessive devitalised tissue, unregulated inflammation and high microbial burden.[6,7] Thus, it stands to reason that wound healing would be optimised by using multimodal therapies that simultaneously control bacterial burden, decrease tissue inflammation, support the ECM and establish a balanced healing environment.

Since antiquity, animal fats and vegetable oils have been widely used in therapeutic applications and for medicinal purposes.[8] Fatty acids (FAs) are membrane phospholipids that participate in the inflammatory response, having influence on skin structure integrity, tissue regeneration and immunological status to support wound healing from inflammation to repair.[9] The effects of various FAs have been demonstrated to promote wound healing through induction of cell migration and angiogenesis, as well as through promotion of antioxidant and anti-inflammatory metabolites.[9] Animal studies evaluating the systemic effects of essential FAs are available in the literature. In one such investigation, Lania et al.[10] found that rat wounds treated with topical FA (sunflower oil) had higher levels of insulin-like growth factor (IGF)-1, a known mitogenic influence on keratinocytes, and increased interleukin (IL-6) levels, a proinflammatory cytokine that resolves inflammation, than the control animals.[10] The ability of FAs to control the invasion of microorganisms and avoid the development of infection during wound repair promotes healing and makes them attractive for therapeutic use in topical wound treatments.[11] Although, to date, there is a paucity of clinical studies investigating the effects of FA administration (topically or orally) in the treatment of hard-to-heal wounds in human subjects.

Of particular interest, omega-3, -6 and -9 FAs have been shown to play a significant role in skin repair by reducing transepidermal water loss, improving skin hydration, regenerating the damaged skin lipid barrier and stabilising skin metabolism.[12] An anhydrous conformable sheet wound matrix containing cold water fish omega FA peptides and

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other non-cytotoxic components is commercially available in the US. The matrix is designed to conform to the wound bed, achieving intimate contact with the surface, ultimately absorbing into the wound during the natural healing process. The potential biological effects of this omega FA-containing wound matrix could have wide utility in the treatment of hard-to-heal wounds of the lower extremity.

In this prospective, single-site pilot case series the author evaluated the effectiveness of this novel marine omega FA-containing multimodal wound matrix (MWM) (OCM; Omeza, US) in reducing bacterial contamination and supporting WAR in patients with hard-to-heal wounds of varying aetiologies. It was hypothesised that weekly application of MWM would result in a reduction of wound bed bacterial levels and a decrease in total wound area. A fluorescence imaging device (MolecuLight i:X; MolecuLight Inc., Canada) was used to objectively measure the bacterial contamination on the surface of the wound bed at each treatment visit, as well as to take standard wound images and digital measurements.

Fluorescence imaging is a validated tool to rapidly provide diagnostic information on the presence and location of moderate-to-heavy bacterial loads in wounds and surrounding tissues that would not otherwise be visible with the naked eye. Clinical trials have shown that endogenous, red fluorescence emitted from porphyrins in bacteria and cyan fluorescence in the presence of *Pseudomonas* bacteria enable the MolecuLight i:X to visualise and locate bacteria present at loads >10^4 colony forming units (CFU)/g on and beneath the surface of wounds up to ~1.5mm deep.[13]

Methods

Patient recruitment

A total of three patients from the author's clinical practice, >18 years old and having hard-to-heal (>4 weeks' duration) open wounds of the lower extremity, were enrolled.

Ethical approval and patient consent

Ethics Board approval from Richmond Heights Wound Center, Ohio, US was not required for this case study. The study was conducted in accordance with Health Insurance Portability and Accountability Act guidelines, adhered to the tenets of the International Conference on Harmonization E6 Good Clinical Practice (ICH GCP) and the Declaration of Helsinki. Before study enrolment, all patients provided written informed consent to publish case details and associated deidentified image assessments. This was not a blinded study. No compensation was provided for participation.

Wounds

Patients had a variety of hard-to-heal wound aetiologies, including two venous leg ulcers (VLUs) and one diabetic foot ulcer (DFU). All wounds were considered non-healing prior to inclusion as they had failed to achieve at least 50% WAR after at least four weeks of treatment with standard of care. Previous wound management had varied and included debridement, offloading, compression bandages, alginates, collagen, gelling hydrofibres and foam dressings. All patients had an ankle–brachial pressure index >0.9mmHg and ≤1.3mmHg. No patients showed any clinical signs or symptoms of wound infection based on the International Wound Infection Institute checklist.[5]

Wound measurement and fluorescence imaging

Fluorescence and standard wound photographs and measurement were obtained weekly via a fluorescence imaging device. The device also contained digital wound area measurement software that automatically detected the wound border and generated instant, accurate wound measurements (wound surface area, length and width).[14]

Wound assessment and treatment

All patients were seen once weekly in the author's clinic for wound assessment and dressing changes. Baseline and weekly fluorescence and standard wound images were obtained. All wounds were debrided to remove devitalised tissue at the clinician's discretion. The MWM was applied once weekly to each patient's wound according to the manufacturer's instructions for use and covered with a primary inert dressing material to manage exudate and promote a moist wound healing environment. The DFU was offloaded via total contact cast and multilayer compression bandages were used in the treatment of the VLUs.

Results

In this case series, two male patients and one female patient participated, and included one DFU and two VLUs. The mean baseline wound age prior to study

Table 1. Age, sex, wound type, wound age, number of treatments and negative fluorescence results of each patient

Patient number	Age, years	Sex	Wound type	Wound age, weeks	Number of treatments	Wound base negative fluorescence, weeks
1	57	M	DFU	24	6	2
2	95	F	VLU	35	4	2
3	64	M	VLU	12	3	2

DFU—diabetic foot ulcer; F—female; M—male; VLU—venous leg ulcer enrolment was 24 weeks, with a mean baseline wound size of 8.61cm^2. Patient demographic information is presented in Table 1.

The two VLUs progressed to complete closure, Patient 3 at visit 3 (Fig 1j) and Patient 2 at visit 4 (Fig 2j). The DFU displayed a total WAR of 53% at six weeks when Patient 1 was lost to follow-up due to a geographical relocation; however, we included the patient data in this analysis (Figs 3a–j). The mean percentage area reduction of all wounds combined was 82% upon study completion. Healing trajectory results are represented in Fig 4.

Fluorescence imaging showed clearance of pathological levels of bacterial contamination in the wound base by week 2 (Table 1). However, fluorescence of the periwound skin, which was not treated with the MWM, was observed to persist. Additionally, wounds remained free of clinical evidence of infection over the entire course of the study for all patients (Figs 1–3).

Discussion

As far back as 2800 BCE, the Babylonians boiled animal fats with wood ashes to obtain soap-like substances. These soaps are one of the oldest known uses of FAs as surfactants.[15] In 1881, investigations by Koch illustrated that FAs had benefit beyond soaps and cleaning agents. Through his studies, Koch established the value of FAs as antibacterial agents, noting that these agents can prevent bacterial growth and directly kill bacteria by inserting directly into the bacterial membrane.[16] Subsequently, the bactericidal effects of FAs gained importance in medicine. Although FAs have been recognised for their antibacterial properties for decades, they have been underused, most likely due to the widespread use of prescription antibiotics in the practice of modern medicine. With a rise in global antimicrobial resistance, alternative antimicrobial agents with no known resistance are of increasing importance.[17] Once again, FAs for use as antimicrobial agents are of particular interest due to their effectiveness, abundance and affordability.

The utility of animal fats and oils for other medicinal purposes has been recognised for the past 50 years.[18] The rich FA concentration found in fish oils makes this source one of particular interest. Potential health benefits of fish oils have been linked to the large amounts of polyunsaturated FAs (PUFAs) found in these oils. Docosahexaenoic acid and eicosapentaenoic acid, which are long-chain omega-3 FAs, are the predominant PUFAs derived from fish oils.[19] Studies on the systemic effects of fish oils gained momentum after widespread reports on the low incidence of inflammatory and heart diseases observed in the Inuit and Yupik populations.[20] It was postulated that this finding was directly related to the diet of the Inuit and Yupik peoples, which is high in fish oils.[20] In response, fish oil FAs have proved to be advantageous in the treatment of conditions, such as heart disease, rheumatoid arthritis, diabetes, ulcerative colitis, asthma, pulmonary dysfunction and Parkinson's disease.[21]

Fig 1. Patient 3. Venous leg ulcer. Wound at treatment visit (TV) 1 pre-debridement (pre) **(a)**; fluorescence image at TV1 (pre) **(b)**; wound measurement at TV1 (pre) **(c)**; wound at TV1 post-debridement (post) **(d)**; fluorescence image at TV1 (post) **(e)**; wound at TV2 (pre) **(f)**; fluorescence image at TV2 (pre) **(g)**; wound measurement at TV2 (pre) **(h)**; fluorescence image at TV2 (post) **(i)**; healed wound at TV3 **(j)**

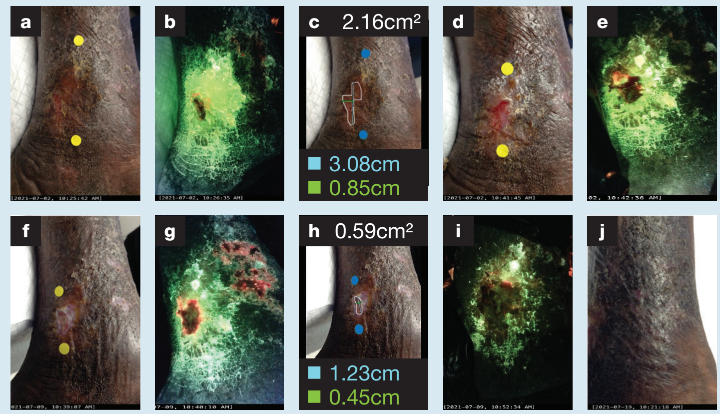
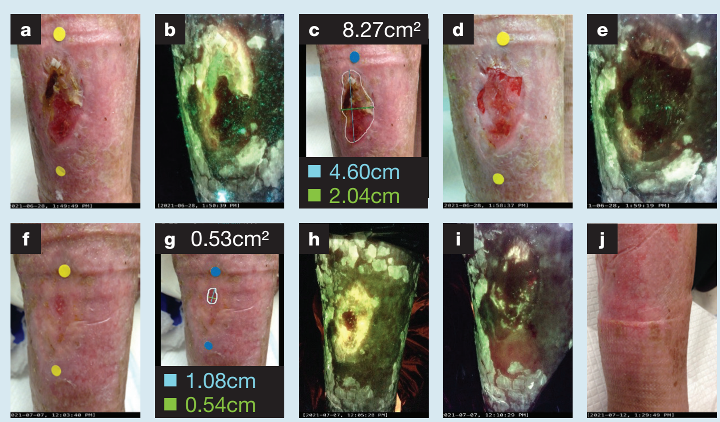


Fig 2. Patient 2. Venous leg ulcer. Wound at treatment visit (TV) 1 pre-debridement (pre) **(a)**; fluorescence image at TV1 (pre) **(b)**; wound measurement at TV1 (pre) **(c)**; wound at TV1 post-debridement (post) **(d)**; fluorescence image at TV1 (post) **(e)**; wound at TV2 (pre) **(f)**; wound measurement at TV2 (pre) **(g)**; fluorescence image at TV2 (pre) **(h)**; fluorescence image at TV2 (post) **(i)**; healed wound at TV4 **(j)**



In the last two decades, there has been increasing research studying the effects of PUFAs in the field of dermatology and in the cosmetic industry. Of note, skin barrier function is limited when a lack of PUFAs is found within the skin.[22] The end result is a disruption in the epidermis, leading to an increase in transepidermal water loss.[22] Additionally, lack of PUFAs in the skin induces an upregulation of inflammatory-related keratin (K17) in the basal cells of the epithelium.[23] Overexpression of K17 is known to lead to a variety of skin conditions including psoriasis.[23] Cytokine generation and function are also regulated by PUFAs.[24] Proinflammatory cytokines play a pivotal role in wound healing, and thus the use of

Fig 3. Patient 1. Diabetic foot ulcer. Wound at treatment visit (TV) 1 pre-debridement (pre) **(a)**; fluorescence image at TV1 (pre) **(b)**; wound measurement at TV1 (pre) **(c)**; wound at TV1 post-debridement (post) **(d)**; fluorescence image at TV1 (post) **(e)**; wound at TV4 (pre) **(f)**; fluorescence image at TV4 (pre) **(g)**; wound measurement at TV4 (pre) **(h)**; wound at TV4 (post) **(i)**; fluorescence image at TV4 (post) **(j)**

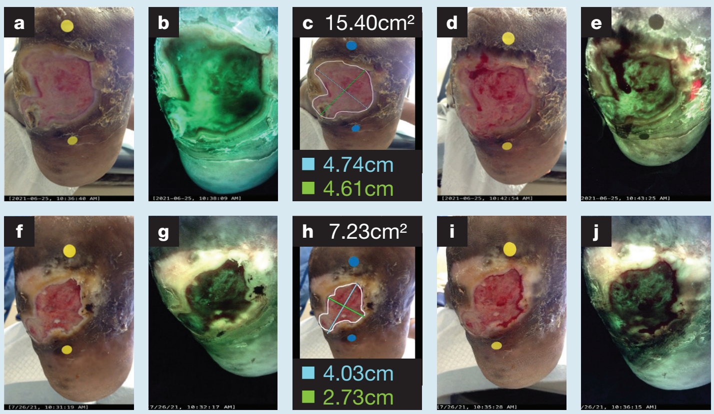
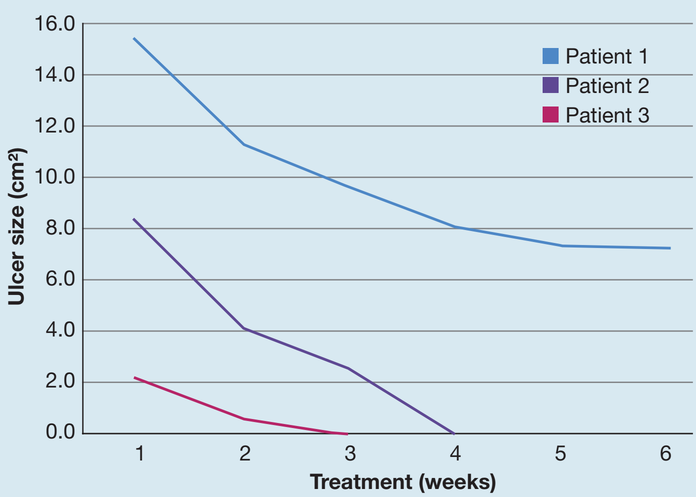


Fig 4. Wound healing trajectory



PUFA-containing products has the potential to bolster the essential cellular processes necessary for tissue repair and regeneration.

There are a wide variety of wound dressings and skin replacement products available to aid in wound healing, although there remains a need for safe and efficient topical therapies in wound management. A key to successful wound management is regulating the appropriate level of inflammation to foster cellular migration. Fish-derived FAs, such as omega-3, -6 and -9, have the potential to attenuate the extended inflammatory phase observed in hard-to-heal wounds.

Despite evidence indicating the successful application of fish oil and omega FAs on a variety of skin disorders, there has been a lack of clinical studies investigating the use of FAs in wound management. Wu and Goldman[25] published the results of a 34-patient randomised controlled trial showing that the use of a topical FA treatment (linolenic acid) after CO_2 laser treatment led to an increase in keratinocyte proliferation and epidermal tissue formation in the treatment cohort. In addition, patients receiving the FA had a decrease in oedema and itching by post-procedure day 3.[25] It is not unreasonable to extrapolate that the results of this study could also be applied to the management of hard-to-heal wounds.

The MWM investigated in this three-patient case series is an anhydrous, amorphous solid formulated for topical application to wounds. The product is a combination of cold water fish peptides, cod liver oil, plant-derived polyunsaturated FAs, medium chain triglycerides, and other plant oils and waxes. It is hypothesised that the FAs contained in this product successfully modulated the inflammatory response in the wounded tissues, thus accelerating the healing rate of otherwise stalled wounds. The impact of the MWM on wound progress is in agreement with in vitro studies on the utility of PUFAs in cosmetic and dermatological use.[26] It has been established in the literature that FAs are potent antimicrobial/microbicidal agents in vitro that can kill enveloped viruses, Gram-positive and Gram-negative bacteria, and fungi on contact.[27] Thus, the author postulates that the FAs found within the MWM used in this case series were able to disrupt the bacterial cell membrane to promote solubility or lysis, leading to the decrease in bacterial contamination levels observed on fluorescence imaging throughout the treatment phase of this study.

Limitations

The major limitations of this pilot study are that it is a single-site, single-arm case series on a very small number of patients. The study period was also limited, with one patient being lost to follow-up. However, the results of this case series lend credence to the idea that the MWM supports wound healing in hard-to-heal lower extremity wounds of varying aetiologies. Future studies should include larger recruitment and a longer duration of follow-up.

Conclusion

In this case series, the use of MWM proved to be effective and safe. The wounds included in this study were stalled in the inflammatory stage with no signs of healing. MWM supported wound closure and reduced bacterial loads in this patient cohort. Topically applied formulations of marine-derived FAs via anhydrous sheet matrices have been developed for wound management. These innovative products have the potential to impact the landscape of topical wound therapies. **JWC**

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Reflective questions

- How can fatty acid-containing products be used in wound management?
- Which hard-to-heal wound aetiologies could benefit from the use of anhydrous, amorphous solid matrices?
- How can products such as the multimodal wound matrix fit into antimicrobial stewardship programmes?

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