An estimated 2% of the US population suffers from chronic wounds resulting from diabetes mellitus, venous insufficiency, and excessive pressure.1 It is estimated that 15% of patients with diabetes have foot ulcers, one in 150 patients with diabetes will undergo an amputation, and 84% of these amputations were related to a simple ulcer that did not heal.2 Significant clinician time and hospital resources are consumed in the outpatient setting by patients with chronic wounds,3,4 causing morbidity, decreased quality of life, and economic strain on the healthcare system. While a variety of approaches exist to treat chronic wounds, evidence-based information is limited regarding how to best treat chronic wounds, when to initiate treatment, and for how long. Evidence-based medicine5 is fast becoming a requirement in wound care, with clinicians demanding evidence before the introduction of new products or a change in wound care practices.6

Ultrasound is a form of mechanical energy transmitted through and into biological tissues as an acoustic pressure wave at frequencies above the limit of human hearing. Ultrasound is thought to produce a number of biophysical effects relevant to wound healing, perhaps by stimulating cellular activity and protein synthesis — processes that are crucial for tissue repair.7 Although ultrasound has been used therapeutically for many years for a wide variety of soft tissue disorders,8-13 wound care clinicians are only recently becoming aware of the role of ultrasound in the healing of incisional lesions,14 diabetic ulcers,15 and venous ulcers.16

Figure 1. The MIST Therapy system.

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The MIST Therapy® System (Celleration, Inc, Eden Prairie, Minn) (see Figure 1) is a low-frequency, noncontact ultrasound therapy that uses acoustic pressure transmitted by ultrasound to stimulate cells\(^\text{1,17,18}\) and remove bacteria.\(^\text{19,20,21}\) Ultrasound activates inflammatory cells, which results in wound debridement and the production of chemical mediators that activate fibroblasts (see Figures 2,3).\(^\text{22,23}\) This leads to the accumulation of endothelial cells in tissues and the promotion of collagen synthesis via stimulated calcium influx, altered membrane permeability, and enhanced fibroblast proliferation. In addition, it has been hypothesized that the application of micromechanical forces to wounds can promote wound healing by fostering cell division, angiogenesis, and local elaboration of growth factors, as well as decreasing matrix metalloproteinase activity.\(^\text{24-26}\) Kavros and Schenk\(^\text{20}\) were able to demonstrate cell wall destruction of bacteria following application of noncontact, low-frequency ultrasound therapy (see Figure 4). Taken in the aggregate, these biophysical and bactericidal effects provide a likely rationale for the use of therapeutic ultrasound at each stage of the wound-healing process.\(^\text{27}\)

One type of ultrasound therapy (MIST\textsuperscript{®}) replaces the coupling gel required for the ultrasound used for fetal monitoring, sports medicine, and physical therapy. It creates low-frequency ultrasound waves that produce and propel a gentle mist of sterile saline to the wound bed, which improves the transfer of ultrasound from the device to the wound bed without pain to the patient.\(^\text{28}\) This is an important consideration for patients who may not be able to withstand the pain of traditional debridement. The atomized mist promotes surface cavitation and microstreaming, which may cause the release of necessary cellular components to stimulate the natural cascade of wound healing.\(^\text{29}\)

This therapy system received Food and Drug Administration 510(K) clearance in June 2005 to “promote wound healing through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates, and bacteria.” It has been approved for use in a variety of wounds, including acute and chronic wounds; diabetic foot, arterial, venous insufficiency, and pressure ulcers; colonized wounds; and burns. As reported by Ennis et al, \(^\text{15}\) the device is easy to use and has produced no serious adverse events throughout preclinical or human studies.\(^\text{1,15,18,20,28,30}\) Contraindications include any use: 1) near electronic implants/prostheses (near or over the heart or thoracic area if the patient

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**Figure 2.** Acoustic energy deforming fibroblasts. Ultrasound activates inflammatory cells that play a role in the production of chemical mediators that activate fibroblasts.

**Figure 3.** Wound debridement. Ultrasound activates inflammatory cells, which results in wound debridement.

**Figure 4.** Cell wall destruction of *Staphylococcus aureus* following application of ultrasound therapy.
has a cardiac pacemaker); 2) on the lower back during pregnancy or over a pregnant uterus; and 3) over areas of malignancies.

Data from published preclinical and human studies continue to suggest that this ultrasound system can significantly promote healing and reduce the time to healing of lower-extremity wounds. A noncomparative clinical outcomes trial of 23 patients from a single tertiary-referral, hospital-based wound clinic evaluated the incidence of wound closure for chronic, nonhealing, lower-extremity wounds of various etiologies using this system. Chronic wounds receiving this therapy as a stand-alone device or in combination with moist wound care were healed in 69% of cases; healing response was evident within 4 weeks of therapy. Ennis et al. also reported the results of a randomized, controlled, double-blind study of patients with diabetic foot ulcers. In addition to standard care, patients received either ultrasound or a sham treatment. Patients receiving ultrasound therapy achieved statistically significant greater healing outcomes when compared with sham therapy (40.7% versus 14.3% at 12 weeks, respectively; \( P = .0366 \)) (see Figure 5). In an open-label, nonrandomized, baseline-controlled clinical case series of 51 patients with lower extremity ulcers, the mean treatment time of wounds was 9.8 ± 5.5 weeks (standard of care) versus 5.5 ± 2.8 weeks (low-frequency ultrasound; \( P < .0001 \)). The mean percent volume reduction was 37.3% ± 18.6% (standard of care) versus 94.9% ± 9.8% (low-frequency ultrasound; \( P < .0001 \)). In a randomized, controlled study of 35 patients with nonhealing leg and foot ulcers associated with chronic critical limb ischemia who received ultrasound therapy plus the standard of wound care (treatment group) versus 35 patients who received the standard of wound care alone (control group), Kavros et al. found that a significant number of patients in the treatment group achieved greater than 50% wound healing at 12 weeks than those in the control group (63% versus 29%, respectively, \( P < .001 \)) (see Figure 5).

**Limitations/Promise of Research**

Approximately 200 patients have participated in initial trials of MIST Therapy. Although impressive, this is a relatively small number for new therapies and additional studies are warranted as this modality is used more widely. It should be noted that Ennis et al. found no significant difference between the intent-to-treat and the sham treatment groups. The researchers believe that this was due to a protocol inconsistency at three sites; prompting a study-wide clinical audit. During the audit, five centers were found to be inverting the treatment distances described in the protocol. The patients at these sites were subsequently disqualified for inclusion in the analysis, leading to a final efficacy population of 55. This treatment group showed a statistically significant difference in wound healing compared with the sham group (\( p=.0366 \)). In light of these protocol inconsistencies, it is imperative that ongoing staff training at clinical study sites continues to be a priority.

**Conclusion**

Based on promising results from preclinical and clinical data, noncontact ultrasound therapy appears to have the potential to improve wound healing and shorten healing times in patients with wounds of the lower extremities. It also may be possible to decrease...
the bacterial burden of chronic wounds; thereby reducing the need for antibiotics, narcotic analgesics, other wound care approaches, and/or readying the wound bed for advanced wound-healing modalities, such as bioengineered skin substitutes. It is hoped that this case series will foster conversation and observations about the impact of this interesting therapy within the wound care community.

References