Clinical Review Criteria

Low Frequency, Noncontact, Nonthermal Ultrasound Wound Therapy (Ultrasonic MIST Therapy)

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Criteria
See the wound care treatment criteria.

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Background
Chronic wounds, wounds with long healing time, and wounds with frequent recurrence are a major health problem. They are a problem for the patient who suffers from them, the clinician who treats them, and the health care system that is overburdened by their cost. It is estimated that chronic wounds affect approximately 2% of the American population at an estimated cost of US $20 billion per year. Many factors can impede wound healing, including chronic disease, venous insufficiency, arterial insufficiency, neuropathy, nutritional deficiencies and local features such as pressure, edema, and infection (Fonder, 2008, Rizzi 2010).

No single regimen is universally accepted as the best modality for treating chronic wounds. They are managed through conventional wound care procedures performed by primary care providers, community nurses, pharmacists, and others. In the early 2000s, the concept of wound bed preparation has been proposed as a means of providing a structured and systemic approach to the management of chronic wounds. It is believed to accelerate endogenous healing and/or facilitate the effectiveness of other therapeutic measures. Wound bed preparation involves ongoing wound debridement, management of exudates, and resolution of bacterial imbalance (Schulz 2003, Ramundo 2008).

Wound debridement is defined as the removal of devitalized or contaminated tissue as well as foreign material from the wound bed until healthy tissue is exposed. Efficient debridement reduces the necrotic burden, achieves healthy granulation tissue, and reduces wound contamination and tissue destruction. This can be performed by different enzymatic, autolytic, sharp/surgical, biological, and mechanical techniques. Each has its own advantages and limitations, and the methods that are most efficient at removal of debris, may at the same time be the most detrimental to fragile new growth (Schulz 2003, Beitz, 2005, Ramundo 2008).

Noncontact, low frequency ultrasound therapy was recently introduced as a modality for promoting wound healing through wound cleansing and maintenance debridement. The therapy is thought to produce a number of biophysical effects that are associated with wound healing. These include increased protein and collagen synthesis, angiogenesis, production of growth hormone by macrophages, endothelial production of nitric oxide synthesis; and leukocyte adhesion. One of the
main mechanisms of action for ultrasound therapy, as shown by in vitro studies, is achieved through the process of cavitation. This involves the production and vibration of micron-sized bubbles within the coupling medium and fluids in the tissues. As the bubbles collect and condense, they are compressed before moving to the next area. This movement and compression can potentially cause changes in the cellular activities of the tissues subjected to the ultrasound. Acoustic streaming is another mechanism by which ultrasound generates biologic activity producing a unidirectional movement of fluid along and around cell membranes. A more recent hypothesis known as the frequency resonance theory uses the above concepts at the protein and genetic level, and result in a broad range of cellular effects that promote healing. Ultrasound energy is also believed to have a direct bactericidal action caused by the cavitation effects produced by the ultrasound waves (Ennis 2005 Ramundo 2008).

The sound waves generated by the therapeutic ultrasound devices have lower frequencies than those generated by diagnostic devices (25-40 kHz vs. 200,000-400,000 kHz respectively). Ultrasound MIST therapy devices use saline to couple the ultrasound energy to tissue within the wound bed. This is accomplished by the noncontact non-thermal application of a fine oxygenated fluid (sterile saline) stream spray to the wound bed through which the ultrasound energy is transmitted from the applicator tip to the wound tissue. This noncontact ultrasound is believed to provide cellular stimulation, increase blood flow, and reduce bioburden with much less pain or thermal effect than other direct contact devices. It is usually applied three times a week for a duration dependent on the wound dimensions. The therapy should be performed in a closed environment area to avoid spread of microbes, and the clinician delivering the therapy should wear protective gear (Ramundo 2008, FDA webpage).

Ultrasound MIST therapy (Celleration, Inc, Eden Prairie, MN), was cleared by the FDA in 2004 to promote healing of wounds through wound cleansing and maintenance debridement by the removal of yellow slough, fibrin, tissue exudates and bacteria. Its use is contraindicated for malignant wounds, radiation wounds, for tissue previously treated with radiation, and for patients with bleeding disorders, or thrombophlebitis.

### Medical Director Clinical Review and Policy Committee Decision

<table>
<thead>
<tr>
<th>Date</th>
<th>Evidence Conclusion</th>
<th>Outcome</th>
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<td>03/02/2010</td>
<td>The committee decision was to not cover this service based on the lack of sufficient evidence to support use of this technology in treatment of wounds.</td>
<td>The use of Low frequency, noncontact, nonthermal ultrasound therapy for the treatment of wounds does not meet the Group Health Medical Technology Assessment Criteria.</td>
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### Medical Technology Assessment Committee (MTAC)

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<tr>
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<td>02/01/2010</td>
<td>The literature search revealed two published RCTs on the low frequency noncontact ultrasound therapy for the treatment of wounds. The two trials were funded by the manufacturer.</td>
<td>The use of Low frequency, noncontact, nonthermal ultrasound therapy for the treatment of wounds does not meet the Group Health Medical Technology Assessment Criteria.</td>
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<td>In one trial, Ennis and colleagues, 2005, compared the ultrasound therapy to a sham device for the treatment of patients with diabetic foot ulcers. Patients in the two treatment groups also received wound conventional therapy. The trial was randomized and controlled, and had clinically important outcome. However, it had several methodological flaws which limit generalization of its results. The study had a very low completion rate (41%) due to dropouts or violations of the protocol, and the ulcers in the sham treatment group were significantly larger in size and with a longer duration than those in the investigational group, which are potential sources of bias and confounding. The results show significant difference in the wound closure favoring the ultrasound therapy group when the analysis included only those who completed the trials, but no significant differences were observed when the analysis was based on intention to treat.</td>
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<td>Kavros and colleagues, 2007, compared the effects of the</td>
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ultrasound therapy plus standard wound care to standard wound care alone in 70 patients with non-healing ischemic lower-extremity wounds. The trial was also randomized and controlled, but was not blinded, and the outcomes were mainly based on measurements which are subject to potential error, and observational bias. Moreover, the authors did not discuss if there were any dropouts, rate of compliance, or adverse events associated with the intervention. Overall, the results of the trial show that patients managed with MIST therapy in addition to standard treatment, achieved a significantly higher >50% wound closure rate in 12 weeks than those managed with standard therapy alone. A secondary analysis of the trial showed that patients with critical limb ischemia with baseline TcPO2 <20 with dependency were significantly less likely to achieve >50% healing by week 12, using standard treatment with or without MIST therapy.

In conclusion, the published literature does not provide sufficient evidence to determine that non-thermal, noncontact, low frequency ultrasound therapy “Mist therapy” is safe to use, or that it has similar or better outcomes than those achieved by other debridement methods or standard wound care management procedures.

**Evidence/ Source Documents**

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<tr>
<th>Date of Literature Search</th>
<th>Articles</th>
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