Non-Contact Ultrasound Treatment for Wounds

Policy Number: 2.01.79  Last Review: 1/2018
Origination: 1/2008  Next Review: 7/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for non-contact ultrasound treatment for wounds. This is considered investigational.

When Policy Topic is covered
Not Applicable

When Policy Topic is not covered
Non-contact ultrasound treatment for wounds is considered **investigational**.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With any wound type (acute or nonhealing)</td>
<td>• Noncontact ultrasound therapy with standard wound care</td>
<td>• Standard wound care</td>
<td>• Symptoms</td>
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<td></td>
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<td>• Change in disease status</td>
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<td></td>
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<td>• Morbid events</td>
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<td>• Quality of life</td>
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<td>• Treatment-related morbidity</td>
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</table>

Low-frequency ultrasound in the kilohertz range may improve wound healing. Several noncontact low-frequency ultrasound (NLFU) devices have received regulatory approval for wound treatment.

For individuals who have any wound type (acute or nonhealing) who receive noncontact ultrasound therapy, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. The single double-blinded, sham-controlled randomized trial, which included patients with nonhealing diabetic foot ulcers, had substantial methodologic flaws (eg, high dropout rate, baseline differences between groups) that limit the validity of the findings. In the remaining studies comprising the evidence base, all but 1 RCT comparing NLFU with standard wound care had improved (statistically significant) results on the primary outcome with NLFU. However, these studies also had
several methodologic limitations. In terms of outcome assessment, complete healing is generally considered the most clinically relevant outcome; a 50% reduction in wound area over time and time to heal are also considered acceptable outcomes. A majority of trials included patients with venous leg ulcers. None of the RCTs evaluating venous leg ulcers reported complete healing or another acceptable outcome as its primary outcome measure, and none had blinded outcome assessment. Only 1 RCT, which addressed split-thickness graft donor sites, reported on the proportion of patients with complete healing and had blinded outcome assessment. Another limitation of the body of evidence is that some standard of care interventions involved fewer visits than the NLFU intervention, and the differences in intensity of care resulting from this differential in face-to-face contact could partially explain the difference in findings between intervention and control groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Background**

Ultrasound (US) delivers mechanical vibration above the upper threshold of human hearing (>20 kHz). US in the megahertz range (1-3 MHz) has been used to treat musculoskeletal disorders, often by physical therapists. Although the exact mechanism underlying its clinical effects is not known, therapeutic US has been shown to have a variety of effects at a cellular level, including angiogenesis, leukocyte adhesion, growth factor, collagen production, and increases in macrophage responsiveness, fibrinolysis, and nitric oxide levels. The therapeutic effects of US energy in the kilohertz range have also been examined. Although the precise effects are not known, low-frequency US in this range may improve wound healing via the production, vibration, and movement of micron-sized bubbles in the coupling medium and tissue.

The mechanical energy from US is typically transmitted to tissue through a coupling gel. Several high-intensity US devices with contact probes are currently available for wound débridement. Low-intensity US devices have been developed that do not require coupling gel or other direct contact. The MIST Therapy System delivers a saline mist to the wound with low-frequency US (40 KHz). A second device, the Qoustic Wound Therapy System, also uses sterile saline to deliver US energy (35 KHz) for wound débridement and irrigation.

The primary end points of interest for trials of wound closure are as follows, consistent with guidance from the U.S. Food and Drug Administration for industry in developing products for treatment of chronic cutaneous ulcer and burn wounds:

1. Incidence of complete wound closure.
2. Time to complete wound closure (reflecting accelerated wound closure).
3. Incidence of complete wound closure following surgical wound closure.
4. Pain control.
Regulatory Status
In 2005, the MIST Therapy® device (Celleration) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process “to promote wound healing through wound cleansing and maintenance débridement by the removal of yellow slough, fibrin, tissue exudates and bacteria.” In February 2015, Celleration was acquired by Alliqua Biomedical (Langhorne, PA).

In 2007, the AR1000 Ultrasonic Wound Therapy System (Arobella Medical, Minnetonka, MN) was cleared for marketing by FDA through the 510(k) process, listing the MIST Therapy® system and several other ultrasonic wound débridement and hydrosurgery systems as predicate devices. The AR1000 system probe uses “contact or noncontact techniques to achieve intended wound therapy modalities to promote wound healing.” Indications in the 510(k) summary are listed as “Selective and non-selective dissection and fragmentation of soft and or hard tissue” and “Surgical, excisional or sharp-edge wound debridement (acute and chronic wounds, burns) for the removal of nonviable tissue including but not limited to diseased tissue, necrotic tissue, slough and eschar, fibrin, tissue exudates, bacteria and other matter.” This device is now known as the Qoustic Wound Therapy System™.

Several other devices have been approved as being substantially equivalent to the earlier devices. FDA product code: NRB.

Rationale
This evidence review was originally created in December 2007 and has been updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through December 18, 2016. Following is a summary of the key literature to date.

The literature review focused on randomized controlled trials (RCTs) evaluating whether the addition of noncontact low-frequency ultrasound (NLFU) improves wound healing compared with standard treatment alone.

Systematic Reviews
In 2015, Tricco et al published an overview of systematic reviews on treatments for complex wounds, which reviewed multiple therapies including ultrasound. The 2011 Voigt et al review was included, but the 2011 Driver et al review was not (see below). Conclusions related to ultrasound therapy are summarized in Table 1.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Type of Review Available</th>
<th>Level of Evidence</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous ulcer</td>
<td>US</td>
<td>Time to healing/rate of healing</td>
<td>SR w/o MA</td>
<td>Low/moderate quality</td>
<td>No difference</td>
</tr>
<tr>
<td>Venous ulcer</td>
<td>HFUS, LFUS, US</td>
<td>Proportion of patients with healed wounds</td>
<td>SR with MA</td>
<td>High quality</td>
<td>No difference</td>
</tr>
<tr>
<td>Mixed</td>
<td>US</td>
<td>Wound area/size</td>
<td>SR with MA</td>
<td>Low/moderate</td>
<td>Effective</td>
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</table>
Two systematic reviews were published in 2011. An industry-sponsored review by Driver et al considered both controlled and uncontrolled studies on NLFU therapy for treating chronic wounds. Eight studies with at least 4 weeks of follow-up were included; 1 was an RCT and the rest were observational studies. The major limitation of this meta-analysis was that there were no pooled comparisons of NLFU therapy to optimal wound care alone or to an alternative intervention. Thus conclusions cannot be drawn about the incremental benefit of NLFU treatment over optimal wound care alone.

The second systematic review, by Voigt et al (2011), only included RCTs; studies used contact or noncontact ultrasound for treating chronic lower-limb wounds. Five RCTs on NLFU were identified, 1 of which was unpublished. A pooled analysis of 2 sham-controlled trials found a significantly smaller proportion of nonhealed wounds at 3 months in the NLFU group than in the control group (relative risk, 0.74; 95% confidence interval, 0.58 to 0.95; p=0.02). This analysis included the Ennis et al (2005) study (described next), and a study from the 1990s that delivered ultrasound therapy during foot bathing (ie, the study did not use a modern device).

**Randomized Controlled Trials**

One double-blind, multicenter, sham-controlled trial was identified. In 2005, Ennis et al published findings of MIST therapy for recalcitrant diabetic foot ulcers in 133 patients. Patients with were treated with active or sham MIST therapy 3 times per week, with débridement as needed and a weekly evaluation by an independent investigator. Twenty-four patients were lost to follow-up, and data from 54 patients were excluded from analysis due to protocol violations (5 centers inverted the treatment distances for the active and sham devices), leaving 55 (41%) patients for the per-protocol analysis. Investigators reported significant improvement in the active treatment group (11/27 [41%] patients) compared with the control group (4/28 [14%] patients) in the proportion of wounds healed (defined as complete epithelialization without drainage). However, intention-to-
treat analysis showed no difference in wound healing (26% vs 22%, respectively) between the active (n=70) and control (n=63) groups. In addition to the 59% loss to follow-up, there was a difference in the ulcer area at baseline (1.7 cm$^2$ vs 4.4 cm$^2$, respectively) and chronicity of wounds (35 weeks vs 67 weeks, respectively) that favored MIST therapy in the per-protocol groups. Due to the serious limitations of this trial, these results are considered inconclusive.

A number of unblinded RCTs comparing NLFU with standard wound care alone and including at least 25 patients have been published.\textsuperscript{8-13} All RCTs used MIST therapy and, other than 2 trials (Beheshti et al [2014]\textsuperscript{11}; Olyaie et al [2013]\textsuperscript{13}) that did not report a funding source, all were industry funded. One study addressed diabetic foot ulcers, the population included in the 2005 RCT by Ennis et al (discussed above). Four RCTs included patients with venous leg ulcers and 1 RCT evaluated treatment of split-thickness graft donor sites. All studies except that on split-thickness graft donor sites included patients with nonhealing wounds; eligibility criteria included wounds that had not healed after at least 4 weeks. In the White et al (2016),\textsuperscript{10} Gibbons et al (2015),\textsuperscript{8} and Prather et al (2015)\textsuperscript{9} studies, patients and providers were not blinded but outcome assessment was blinded. The other studies did not mention blinding. Standard care interventions varied, but generally consisted of wound cleaning, noncontact dressings, compression and, if deemed necessary by providers, débridement. In 2 studies (White et al, Gibbons et al), authors mentioned following national guidelines for the standard care intervention. Prather et al did not describe the standard care intervention and Beheshti et al reported only that compression was used. Study characteristics and findings are summarized in Table 2.

All but 1 of the RCTs in Table 2 had improved (statistically significant) results for the primary outcome with NLFU than with standard of care. However, these studies had methodologic limitations. In terms of outcome assessment, complete healing is generally considered the most clinically relevant outcome; a 50% reduction in wound area over time and time to heal are also considered to be acceptable outcomes.\textsuperscript{14} A reduction of less than 50%, or wound area reduction without a predefined cutoff, is not considered acceptable. The majority of trials included patients with venous leg ulcers. No trials had blinded outcome assessment, reported complete healing, or used one of the other acceptable measures as its primary outcome. Only 1 RCT (Prather study on split-thickness graft donor sites) met both of these criteria. Another limitation of the body of evidence is that some of the standard care interventions involved fewer visits than the NLFU intervention, and the nonspecific effects of this differential in face-to-face contact could partially explain the difference in findings between intervention and control groups.

\textbf{Table 2: Randomized Controlled Trials Comparing NLFU to Standard Care With at Least 25 Patients}

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Wounds included</th>
<th>Interventions</th>
<th>Primary Outcome and Was Outcome Assessment Blinded?</th>
<th>Results</th>
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<tr>
<td>Study</td>
<td>N</td>
<td>N</td>
<td>Ulcer Type</td>
<td>Treatment Details</td>
<td>Outcomes</td>
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<td>------------------------------------------------------------------------------------</td>
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<tr>
<td>White et al (2016)</td>
<td>36</td>
<td>36</td>
<td>Venous leg ulcers (≥6 wk)</td>
<td>NLFU: 3×/wk for 8 wk (after 2-wk run-in period)</td>
<td>Percent wound area reduction at 13 wk: Yes</td>
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<td></td>
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<td></td>
<td>SOC: &gt;1 visit per week for 8 wk</td>
<td>NLFU + SOC: -46.6% (SD=38.1%)</td>
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<td>SOC: -39.2% (SD=38.0%)</td>
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<td>p=0.565</td>
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<tr>
<td>Gibbons et al (2015)</td>
<td>81</td>
<td>74</td>
<td>Venous leg ulcers (≥30 d)</td>
<td>NLFU: 3×/wk for 4 wk</td>
<td>Percent wound area reduction at 4 wk: Yes</td>
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<td>SOC: &gt;1 visit per week for 8 wk</td>
<td>NLFU + SOC: -61% (SD=28.9%)</td>
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<td>SOC: -45% (SD=32.5%)</td>
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<td></td>
<td>p=0.002</td>
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<td>Beheshti et al (2014)</td>
<td>90</td>
<td>90</td>
<td>Venous leg ulcers (≥4 wk)</td>
<td>NLFU: 3×/wk until healed (same protocol for HFU)</td>
<td>Time to wound healing (months): NR</td>
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<td>SOC: Compression therapy (visit frequency not reported)</td>
<td>NLFU + SOC: 5.70 (SD=1.57)</td>
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<td>HFU + SOC: 6.10 (SD=1.47)</td>
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<td>SOC: 8.13 (SD=1.40)</td>
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<td>3 groups: p&lt;0.001</td>
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<td>HFU vs NLFU: p=0.22</td>
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<td>Olyaie et al (2013)</td>
<td>90</td>
<td>90</td>
<td>Venous leg ulcers (≥4 wk)</td>
<td>NLFU: 3×/wk for 3 mo or until healed (same protocol for HFU)</td>
<td>Time to wound healing (months): NR</td>
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<td>SOC: 3×/wk for 3 mo or until healed</td>
<td>NLFU + SOC: 6.65 (SD=1.59)</td>
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<td>HFU + SOC: 6.86 (SD=2.04)</td>
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<td>SOC: 8.50 (SD=2.17)</td>
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<td>3 groups: p=0.001</td>
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<td></td>
<td>HFU vs NLFU: p=NR</td>
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<tr>
<td>Kavros et al (2007)</td>
<td>70</td>
<td>70</td>
<td>Nonhealing foot, ankle, or leg wounds (≥8 wk)</td>
<td>NLFU: 3×/wk for 12 wk SOC: Daily visits</td>
<td>Proportion of patients with &gt;50% wound healing healed at 12 wk: NR</td>
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<td></td>
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<td></td>
<td>NLFU + SOC: 63%</td>
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<td></td>
<td>SOC: 29%</td>
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<td></td>
<td>p&lt;0.001</td>
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<tr>
<td>Prather et al (2015)</td>
<td>31</td>
<td>27</td>
<td>Split-thickness graft donor sites</td>
<td>NLFU: 1×/wk for 5 consecutive days (after 2-wk run-in period) SOC: 1×/wk for 5 consecutive days (after 2-wk run-in period)</td>
<td>Time to wound healing (days): Yes</td>
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<td></td>
<td>NLFU + SOC: 12.1 (SD=6.0)</td>
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<td></td>
<td></td>
<td>SOC: 21.3 (SD=14.7)</td>
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<td></td>
<td>p=0.04</td>
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</table>

HFU: high-frequency ultrasound; NLFU: noncontact low-frequency ultrasound; NR: not reported; SOC: standard of care.

a Reported this outcome; did not specify primary outcome

**Summary of Evidence**

For individuals who have any wound type (acute or nonhealing) who receive noncontact ultrasound therapy, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are symptoms, change in disease status, morbid events, quality of life, and treatment-related morbidity. The single double-blinded, sham-controlled randomized trial, which included patients with nonhealing diabetic foot ulcers, had substantial methodologic flaws (eg, high
dropout rate, baseline differences between groups) that limit the validity of the findings. In the remaining studies comprising the evidence base, all but 1 RCT comparing noncontact low-frequency ultrasound (NLFU) with standard wound care had improved (statistically significant) results on the primary outcome with NLFU. However, these studies also had several methodologic limitations. In terms of outcome assessment, complete healing is generally considered the most clinically relevant outcome; a 50% reduction in wound area over time and time to heal are also considered acceptable outcomes. A majority of trials included patients with venous leg ulcers. None of the RCTs evaluating venous leg ulcers reported complete healing or another acceptable outcome as its primary outcome measure, and none had blinded outcome assessment. Only 1 RCT, which addressed split-thickness graft donor sites, reported on the proportion of patients with complete healing and had blinded outcome assessment. Another limitation of the body of evidence is that some standard of care interventions involved fewer visits than the NLFU intervention, and the differences in intensity of care resulting from this differential in face-to-face contact could partially explain the difference in findings between intervention and control groups. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Practice Guidelines and Position Statements
In 2010, the Association for the Advancement of Wound Care (AAWC) published guidelines on care of pressure ulcers. Noncontact low-frequency ultrasound therapy was included as a potential second-line intervention if first-line treatments did not result in wound healing.

The AAWC guidelines on treatment of venous ulcers, updated in 2010, states that low-frequency ultrasound treatment requires additional evidence before it can be considered an appropriate treatment.

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

References

**Billing Coding/Physician Documentation Information**

**97610**  
Low frequency, non-contact, non-thermal ultrasound, including topical application(s), when performed, wound assessment, and instruction(s) for ongoing care, per day

**ICD10 Codes**

**E08.621, E08.622,** Various types of diabetes with skin complications (foot ulcer or other skin ulcer) code list  
**E09.621, E09.622,**
E10.621,  
E10.622,  
E11.621,  
E11.622,  
E13.621,  
E13.622  
I83.001-  
I83.029;  
I83.201-  
I83.229  
L00-    
L08.9  
L89.00-  
L89.95  
L97.10-  
L97.929  
L98.41-  
L98.499  
L99  
Varicose veins with ulcer code range  
Infections of the skin code range (includes cellulitis – L03)  
Pressure ulcer code range  
Non-pressure chronic ulcer of skin code range  
Non-pressure chronic ulcer of skin not otherwise classified code range  
Other disorders of skin and subcutaneous tissue in diseases classified elsewhere  

Coding information on the Celleration website states that, “Providers may determine it is appropriate to use the MIST Therapy system in conjunction with or adjunctively to other wound treatment procedures (e.g., surgical or sharp debridement).” (1)

Additional Policy Key Words  
N/A

Policy Implementation/Update Information  
1/1/08  New policy, considered investigational.  
7/1/08  No policy statement changes.  
1/1/09  No policy statement changes.  
7/1/09  No policy statement changes.  
1/1/10  No policy statement changes.  
7/1/10  No policy statement changes.  
1/1/11  No policy statement changes.  
7/1/11  No policy statement changes.  
1/1/12  No policy statement changes.  
7/1/12  No policy statement changes.  
1/1/13  No policy statement changes.  
7/1/13  No policy statement changes.  
1/1/14  New 2014 CPT code. No policy statement changes.  
4/1/14  Removed deleted code 0183T.  
7/1/14  No policy statement changes.  
1/1/15  No policy statement changes.  
7/1/15  No policy statement changes.
No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.