

# Practical Considerations of Using Topical Honey for Neuropathic Diabetic Foot Ulcers: A Review

Jennifer J. Eddy, MD; Mark D. Gideonsen, MD; Gregory P. Mack, DPM

## ABSTRACT

*Context:* It is increasingly important to identify and use low-cost effective dressings for treating diabetic foot ulcers as medical costs and rates of diabetes continue to rise. Honey is an inexpensive moist dressing with antibacterial and tissue-healing properties that has shown promise in the medical literature. Many clinicians are unfamiliar with its use, but patients with diabetic foot ulcers may wish to try honey therapy or discuss it with their physicians. The purpose of this review is to familiarize physicians with practical aspects of using honey to treat diabetic foot ulcers.

*Evidence Acquisition:* The authors have experience using topical honey and are currently conducting a randomized controlled trial of its effectiveness in treating diabetic foot ulcers. In this review, the authors summarize evidence of honey's effectiveness, its hypothesized mechanism of action, potential risks and benefits, the types of honey available, and the nature of its application. Critical aspects of ulcer care are also reviewed.

*Conclusion:* Honey is a low-cost topical therapy with important potential for healing. Its use may be considered in diabetic foot ulcers after a discussion of risks and benefits and in conjunction with standard wound care principles.

## INTRODUCTION

There has been resurgence of interest in the use of topical honey to treat diabetic foot ulcers,<sup>1-4</sup> reflecting a growing awareness of the cost and burden of diabetic foot ulcers and the need for cost-effective therapies. However, clinicians unfamiliar with honey therapy

may feel uncomfortable initiating such treatment or responding to patient questions. This review is a practical guide to the use of topical honey for diabetic foot ulcers (DFUs) for primary care physicians from physicians experienced in the treatment and currently conducting a double-blind randomized controlled trial of its effectiveness.

### *General Considerations*

A comprehensive approach to DFUs must address 3 critical aspects of care: assuring adequate blood supply, eliminating pressure on the ulcer, and assessing for infection.

Poor blood supply is not a contraindication to a trial of honey therapy, but no topical therapy is likely to be successful unless the vascular supply is adequate. Prior to initiating honey therapy, an assessment of the vascular supply to the affected limb should be done. If pulses are palpable, the vascular supply can be presumed adequate.<sup>5</sup> If pulses are not palpable, patients should undergo an Ankle-Brachial Index (ABI). An ABI <.9 is abnormal; an ulcer associated with an ABI <.6 is considered more than moderate risk<sup>6</sup> and may require surgical bypass or vascular stenting in order for the ulcer to heal.

Any pressure on the ulcer is detrimental to healing.<sup>7</sup> Many options for off-loading DFUs are available, including Podus boots, CAM and Crow walkers, and Peg assist insoles. Some patients need complete immobilization with a wheelchair or crutches to ensure that pressure is not put on the wound. Wounds with surrounding callus should be debrided to the outer edge of the hyperkeratotic tissue.<sup>8</sup>

Infection often complicates DFUs and slows wound healing. Redness, swelling, and warmth may be absent in diabetic patients due to a suppressed immune response, thus complicating diagnosis.<sup>9-10</sup> As a result of diabetic peripheral neuropathy, pain is often absent even in the presence of severe infection. A quantitative bacterial load of >10<sup>5</sup> bacteria/g tissue on deep tissue

**Author Affiliations:** Family Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wis.

**Corresponding Author:** Jennifer J. Eddy, MD, Assistant Professor of Family Medicine, University of Wisconsin School of Medicine and Public Health, 617 W Clairemont Ave, Eau Claire, WI 54703; phone 715.855.2037; fax 715.839.5176; e-mail jennifer.eddy@fammed.wisc.edu.

biopsy is diagnostic of infection, as is a positive wound culture from a curettage of the base of the wound performed after debridement.<sup>9</sup> A deep tissue swab after debridement is also acceptable; superficial swabs are unreliable and should not be used. Infected wounds should receive prompt antimicrobial therapy with broad spectrum antibiotics covering Gram positive, Gram negative, and anaerobic bacteria.<sup>9</sup> DFUs should be probed and, if they reach bone, evaluated for osteomyelitis.

#### *Patient Acceptance of Honey*

Some patients may be drawn to honey because of its low cost or as an “alternative” therapy that has been used since Ancient Egypt.<sup>11</sup> Others may feel uncomfortable applying a sticky food substance to their ulcer. A review of 40 patients using honey for venous ulcers showed both positive outcomes and high patient acceptance.<sup>12</sup>

### **EVIDENCE OF EFFECTIVENESS**

Honey is a plausible intervention for diabetic foot ulcers as it has been shown to promote healing in animal models,<sup>13-16</sup> and to eradicate a wide variety of pathogens in the laboratory, including Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and *Pseudomonas*.<sup>17-20</sup> There are impressive case reports of healing in the literature,<sup>21-24</sup> although the number and quality of randomized controlled trials are limited. Reviews of the evidence have been largely positive.<sup>1,25</sup>

#### *Mechanisms of Action*

Honey is hyperosmolar, containing <20% water. The low water content draws fluid both from the edematous wound (improving circulation), and from the bacteria within it, effectively dehydrating them. Honey’s antibacterial properties are not entirely due to hyperosmolarity, however. It is acidic (pH 3.5-5) and contains the enzyme glucose oxidase, which produces a small amount of hydrogen peroxide that kills bacteria without damaging tissue. Flavanoids and phenolic acids isolated from honey further contribute to its antibacterial activity.<sup>26</sup> Since honey’s antibacterial activity is multi-factorial, bacteria are unlikely to develop resistance to it.

In addition to its antibacterial properties, honey has demonstrated tissue-healing properties. It keeps wounds moist, permitting epidermal migration, and provides trace nutrients that may assist healing.<sup>27</sup> Also, recent research has shown that honey stimulates inflammatory cytokines (eg, TN- $\alpha$ , IL-6, IL-1 $\beta$ ) by macrophages.<sup>28-30</sup>

#### *Risks and Benefits*

The primary benefits of honey therapy include low cost and potentially accelerated healing.

The most common risk associated with honey’s use is a burning or stinging sensation due to its low pH.<sup>27</sup> This concern may not be relevant for neuropathic diabetic foot ulcers that result from a lack of sensation.

The most serious potential risk of honey’s use is that of wound infection from spores present in honey, such as *Clostridium* or *Bacillus*.<sup>31</sup> These spores do not germinate in honey but could theoretically result in wound infection if the honey is diluted with wound exudate. This risk appears to be low, and possibly nonexistent. Honey has repeatedly been shown to prevent growth of a wide variety of organisms, even when diluted 10-fold or more.<sup>32</sup> *Clostridium* spores are easily suppressed by the presence of other bacteria with which most diabetic foot ulcers are plentifully colonized. Conditions necessary for the growth of *Clostridium* spores,<sup>33-35</sup> which are absent in honey-treated wounds, include (1) lack of competing bacterial flora, (2) low acid environment, (3) high moisture content, and (4) sugar content <56%. Moreover, over 2000 case reports of topical honey therapy in the medical literature have not yielded a single instance of wound infection caused by these spores.<sup>31</sup>

### **WHICH HONEY TO USE?**

If, after a discussion of risks and benefits, the patient wishes to proceed with honey therapy, the next step is to choose the type of honey. Options are based on both the plant from which the honey is derived and the type of processing used.

All types of honey appear to be effective for wound healing. Honey from different sources has varying antibacterial properties: Manuka or jellybush honey from *Leptospermum scoparium* and Jambhul honey from India exhibit particularly high levels of in vitro bacterial suppression.<sup>36-37</sup> Rarely, honey from certain plants can be toxic when ingested (“mad honey intoxication” associated with honey from *Rhododendron ponticum* grown in Turkey, Japan, Nepal, and Brazil;<sup>38</sup> liver problems or teratogenicity<sup>39</sup> associated with honey from *Senecio jacobaea* or other plants containing pyrrolizidine alkaloids), but these concerns do not extend to honey’s external use.

Processing is different for raw, commercial, and medical grade honeys. Raw honey is minimally processed. It is the least regulated form of honey and has been used in the majority of case reports in the literature.

Supermarket-variety honey is attractive because of its low cost and wide availability, and FDA regu-

lation deeming it safe for ingestion by children and adults. It has proven effective in case reports and the authors' professional experience, and is currently being used in a randomized controlled trial conducted by the authors. As part of the commercial process, honey is typically heated to 110°F for over 8 hours, then flash heated to 175°F before being filtered. Cost range is similar for raw and supermarket honey: under \$15 for 32 ounces.

Two types of medical-grade honey have recently received FDA approval for wound treatment. Medical honey is typically filtered and may or may not be heated; gamma-irradiation is sometimes used to inactivate spores. Honey-impregnated calcium alginate dressings cost \$12 per 2"x2" dressing and \$28 per 4"x5" dressing; gamma-irradiated manuka honey costs about \$64 for 32 ounces.

### *How Should Honey Be Applied?*

The medical literature reports that honey has been applied from 1 to 4 times daily. Honey dressings are designed to be changed even less frequently. There is no evidence to direct optimum frequency of dressing changes. In the authors' current trial, patients apply honey twice daily. A generous amount of honey (enough to cover the wound completely with a thick layer) is placed on a gauze or nonstick dressing, which is then directly applied to the ulcer. Cling gauze is then used to wrap the dressing.

### *How Soon Should Results Be Apparent?*

Wounds should be meticulously measured before beginning treatment, and weekly thereafter. Multiplying the largest length in any direction by the largest perpendicular width is a recommended measurement technique that has proved reliable, especially when performed by the same examiner.<sup>40</sup> As with any therapy for DFU, if the wound is not improving in size and appearance after 2 weeks of therapy, the treatment strategy should be modified.<sup>41</sup> Hyperbaric oxygen therapy and maggot therapy are other options that have proved successful in randomized controlled trials.<sup>42-43</sup> In our experience of using honey, improvement is typically seen in wound appearance and size after 2 weeks of twice daily.

## **CLINICAL EXPERIENCE APPLYING HONEY**

All patients with adequate blood supply and no evidence of osteomyelitis are candidates for honey therapy. Patient interest and suboptimal response to standard therapy have been the most common reasons to initiate honey therapy. The authors typically provide written

material when reviewing the risks and benefits with patients, but do not insist on a formal consent form unless patients are hospitalized or participating in the authors' research protocol. Off-loading and debridement are continued during therapy, although antibiotics are often discontinued. (In the trial, antibiotic use is determined by the patient's primary care physician or the study podiatrist, both of whom are blinded to topical therapy.) The authors typically see patients every week for the first few weeks and then every 2-4 weeks thereafter, depending on the severity of the ulcer. The authors measure the wound and/or trace it on acetate to monitor wound progress over time.

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