



# Topical Antimicrobial Use in Diabetic Wound Healing

These agents are important treatment modalities.

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**A** 2018 retrospective analysis of Medicare beneficiaries identified that approximately 8.2 million people in the United States have wounds with or without infections.<sup>1</sup> Of these 8.2 million wounds, the most expensive ones to treat are surgical and diabetic wounds.<sup>1</sup> Diabetic foot ulcers are commonly encountered problems that pose unique challenges to healthcare practitioners across the globe. In the United States alone, more than 100 million people suffer from diabetes or pre-diabetes.<sup>2</sup> 15-25% of people with diabetes will develop a foot ulceration in their lifetime.<sup>3,5</sup> Of these ulcers, over 50% may become infected.<sup>3</sup> In the five-year span between 2007 and 2013, there were 5.6 billion ambulatory care visits in the United States. Of that, about 785 million involved diabetes and 6.7 million ambulatory care visits were either for diabetic foot ulcers or diabetic foot infections<sup>6</sup> with a management cost of between \$9 to \$13 billion dollars.<sup>7,8</sup>

## Antimicrobials

Antimicrobials are one aspect of diabetic foot ulcer management that can have an impact on patient outcomes. Antimicrobials function to impede the replication of pathogenic organisms in the wound without providing significant damage to host cells.<sup>4</sup> Antimicrobials can be divided into two groups, antiseptics and antibiotics. Antibiotics are chemical compounds that in dilute solutions kill or inhibit micro-organisms.<sup>9</sup> Anti-

biotics can be naturally produced by a micro-organism such as penicillin or vancomycin or synthetically produced, such as the quinolone class of antibiotics. They generally act on one specific cell target and therefore have a narrower spectrum of activity.<sup>4</sup> Antibiotics are relatively non-toxic but are more susceptible to losing their effectiveness to bacterial resistance. Topical antibiotics are generally derived from agents developed

acetic acid, sodium hypochlorite (Dakin's solution), superoxidized water, and polyhexamethylene biguanide.<sup>4</sup> Disinfectants are often applied to intact skin or some open wounds and function to kill or inhibit microorganisms.<sup>4</sup> They also have residual anti-infective activity and are therefore commonly employed as part of the surgical skin preparation in the operating room. However, certain antiseptics have been found to delay the pro-

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for systemic use such as bacitracin, neomycin, polymyxin B, gentamycin, mupirocin, erythromycin, and metronidazole.<sup>9</sup> Current Infectious Diseases Society of America foot infection guidelines recommend against using topical antibiotics that are available for systemic therapy for wound infections.<sup>10</sup> Rationale for this recommendation is that use of topical antibiotics may cause local adverse effects, provoke delayed hypersensitivity reactions, favor super-infections, and help promote emergence of bacterial resistance.<sup>10</sup> One exception is the use of metronidazole, as it reduces the fetid odor of presumably anaerobically colonized wounds.<sup>9</sup>

Antiseptics, on the other hand, are broad-spectrum disinfectants and include hydrogen peroxide, chlorhexidine, silver, honey, cadexomer iodine,

duction of collagen and damage host tissue cells including fibroblasts, keratinocytes and possibly leukocytes.<sup>4</sup>

The use of topical antimicrobials is a common part of therapy for foot ulcers in healthcare settings. As stated by Wang, et al., "clinicians have increasingly recognized the value of choosing suitable dressings to manage diabetic foot ulcers, which can help accelerate wound healing processes, inhibit propagation of microbes, and improve wound healing rate."<sup>11</sup> The high utilization of topical antimicrobial agents and dressings prompted a Cochrane Database Systematic Review assessing the efficacy of topical antimicrobial agents in the healing of diabetic foot ulcers.<sup>4</sup> The 2017 systematic review casted a wide net and included randomized con-

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trolled trials in any setting, on clinically infected or uninfected diabetic foot ulcers, and included any type of antimicrobials, including antiseptics, antibiotics, and antimicrobial dressings. The authors found 22 trials that met the inclusion criteria with a total of over 2,310 participants.

Analysis of the 22 trials revealed with low-level certainty that the use of antimicrobial dressings instead of non-antimicrobial dressings may increase the number of diabetic foot ulcers healed over a medium term follow-up period. The authors also found, with moderate certainty, little difference in the risk of treatment-related adverse events between systemic antibiotics and topical antimicrobials.<sup>4</sup> This article will discuss current evidence for some of the commonly used topical antimicrobials including cadexomer iodine, silver, honey, and polyhexamethylene biguanide in diabetic wound healing.

### Cadexomer Iodine

Iodine is a well-known antimicrobial agent. Iodine has been found to pass through the cell wall of microorganisms and react with groups of amino acids, thereby disrupting the protein structure.<sup>12</sup> By disrupting met-

oposed to molecular iodine, is that the slow release regulates iodine availability, allowing antibacterial properties to exist while reducing toxicity to the wound bed.<sup>12,14</sup> Cadexomer iodine has also been shown to increase production of pro-inflammatory cytokines as well as vascular endothelial growth factor.<sup>14</sup> By increasing vascular endothelial growth factor, cadex-

given the broad spectrum of microbiota present in chronic diabetic wounds.<sup>15,16</sup> Moreover, Iodine has not been shown to cause any significant resistance with microbes despite its widespread use over time.<sup>15</sup>

### Silver-Based Products

Silver impregnated dressings are commonly utilized wound products

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omer iodine can help facilitate the revascularization process of injured tissue, which is a crucial component of wound healing.<sup>14</sup>

Cadexomer iodine appears to work particularly well in reducing microbial load of chronic non-healing diabetic foot ulcers complicated by biofilms.<sup>13</sup> Biofilms are present in the majority of chronic wounds and can delay healing through an elevated inflammatory state that they produce.<sup>13,15</sup> One study by Fitzgerald and colleagues used quantitative microbiology to demonstrate significantly superior effectiveness of cadexomer

in the treatment of diabetic foot ulcers. Silver products function by releasing positively charged cations that bind to bacterial enzymes, cell walls, and DNA, thereby limiting their function and cell replication.<sup>17</sup> Silver kills microbes on contact by inhibiting cellular respiration, denaturing nucleic acid, and altering cellular membrane permeability. In addition to its antimicrobial properties, silver has also been shown to help with wound healing through reduction in wound inflammation.<sup>5</sup> The effectiveness of silver preparations may be dose-dependent.<sup>5</sup> Silver has minimal toxic potential and has been shown to rarely induce microbial resistance.<sup>17</sup> Although silver has minimal adverse effects including argyria and skin irritation, it is generally considered appealing as a wound dressing, hence lending to its widespread use globally.

Contrary to cadexomer iodine, studies have found limited effectiveness of silver in settings of biofilms.<sup>15</sup> This may be because silver “has limited solubility in the presence of physiological salt and is sensitive to inactivation in the presence of serum”.<sup>15</sup> Therefore, wound debridement in instances of biofilm may be especially important when considering application of silver products.<sup>15</sup> One small study involving 25 patients by Sharma et al. demonstrated silver colloidal based dressings had significantly better outcomes with respect to complete healing and decrease in

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abolic enzymes, cellular respiration is halted and the microbe cannot survive.<sup>12</sup> The routine use of iodine in chronic wound care, however, has been an area of much controversy due to potential cytotoxic properties. Moreover, pain and skin irritation have been reported as a side-effect of iodine use. Cadexomer iodine is 0.9% iodine carried in polysaccharide beads.<sup>13</sup> As the polysaccharide beads absorb wound fluid, 0.9% iodine is slowly released, making cadexomer iodine very absorbent and useful in highly exudative wounds. One additional benefit of cadexomer iodine, as

iodine against methicillin-resistant *Staphylococcus aureus* (MRSA) biofilms in comparison with silver and mupirocin dressings.<sup>15</sup>

Further, cadexomer iodine showed strong activity against both gram positive and gram-negative bacterial biofilms. Iodine is thought to work well in biofilms due to its neutral and lipophilic nature, which can provide greater mobility in biological systems.<sup>15</sup> Cadexomer iodine has been shown to be effective against a wide range of bacteria as well as biofilms, and has a low risk profile, making it a potentially useful tool

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size of diabetic ulcers when compared with conventional dressings.<sup>17</sup> In this study, after 12 weeks of dressing changes, complete healing was seen in 84.62% of patients in the silver group and 41.67% of patients in the conventional dressing group.<sup>17</sup>

A prospective study by Al Saeed and colleagues compared the effectiveness of silver and honey dressings in treating neuropathic diabetic foot ulcers in 71 patients.<sup>5</sup> The authors found the mean time to eradicate infection was reduced in the silver treatment group compared to the honey treatment group; however, this difference was not significant.<sup>5</sup> Additionally, a pilot study involving a 31 patient randomized control study by Tsang et al. showed that nanocrystalline silver was potentially superior to manuka honey in healing diabetic foot ulcers in terms of ulcer size and reduction rates.<sup>18</sup> Once again, however, these findings were not significant.

While the outcomes may appear more promising for some of the smaller, more recently published studies, the lack of statistical significance in the literature makes it difficult to confidently justify the use of silver in wound dressings. A 2007 *Cochrane Systematic Review* found silver dressings did not significantly increase complete ulcer healing as compared with standard dressings.<sup>19</sup> The review also noted insufficient evidence to recommend silver dressings or topical silver agents for the treatment of infected or contaminated chronic wounds. Additionally, a separate *Cochrane Review* from 2006 examined use of silver-based wound dressings in diabetic foot ulcers and found that more trials are needed to justify use of silver in diabetic foot dressings.<sup>20</sup>

A 2014 systematic review and meta-analysis published in *American Family Physicians* found that silver failed to speed up healing after reviewing 10 qualifying randomized controlled trials totaling 1,356 patients.<sup>21</sup> The authors recommended against the use of topical silver in the treatment of non-burn wounds with grade A strength corresponding to recommendation based on consistent and good quality patient-oriented evidence.<sup>21</sup>

## **Honey**

Honey has been used since ancient times to treat wounds.<sup>16</sup> While the mechanism of action is not yet fully understood, the antibacterial action of honey is believed to result from a combination of its osmotic effect, its hydrogen peroxide activity, and its acidity.<sup>22,23</sup> Honey is hyperosmolar due to its high sugar content, which functions to restrict the availability of environmental water to bacteria and other organisms leading to cell disruption and death.<sup>5,15,22</sup>

Hydrogen peroxide in honey functions to clean wounds and protect against infection.<sup>11</sup> However, some honeys, especially *Leptospermum* or manuka varieties, retain bactericidal properties even without the presence of hydrogen peroxide.<sup>16</sup> The acidic nature of honey inhibits the growth of most microorganisms.<sup>5</sup> Honey has a mean pH of 4.4 and most wounds are accompanied by a pH of

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greater than 7.3.<sup>22,11</sup> Honey has been shown to be effective against gram positive, gram negative, aerobic, and anaerobic bacteria, making it useful in many clinical scenarios.<sup>16</sup>

Honey has been noted to have anti-inflammatory effects through the presence of naturally occurring phytochemicals.<sup>5,22</sup> These include antioxidants, such as flavonoids, monophenolics, polyphenolics, and vitamin C that can function to counteract inflammation commonly seen in chronic wound settings.<sup>22</sup> For example, flavonoids in honey have been shown to counteract oxidative stress resulting from advanced glycation end products in dia-

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betic wounds.<sup>18</sup> This is important, as “the accumulation of advanced glycation end products causes upregulation of pro-inflammatory cytokines” making it difficult for the wound to heal.<sup>18</sup> Similar to cadexomer iodine, honey works well in different biological settings. It has been shown to provide rapid autolytic debridement and wound deodorization.<sup>22</sup> The moist environment provided by honey is optimal for wound healing.<sup>5</sup>

Further, this moist environment can help minimize hypertrophic scarring.<sup>22</sup> In general, honey has minimal to no risk profile. There have been occasional reports of stinging pain after administration of topical honey, making it difficult for some patients to tolerate.<sup>23</sup> One potential risk of using honey in a medical setting is contamination with botulinum spores. If a wound was contaminated with botulinum spores in an anaerobic environment, proliferation of spores and production of botulinum toxin could occur, potentially leading to serious effects such as paralysis and cardiac arrhythmia.<sup>22</sup> This is unlikely in a clinical setting, as medical honey has been treated with gamma irradiation that destroys spores seen in honey while preserving its beneficial properties.<sup>22</sup>

In a meta-analysis by Wang, et al., honey dressings “effectively shortened the wound debridement time, wound healing time, and bacterial clearance time” in diabetic foot ulcers.<sup>11</sup> However, this systematic review was limited in that only 11 studies fit the selection criteria. The authors stressed the importance of more prospective, large-scale studies involving honey to better evaluate the effectiveness of this dressing type moving forward.<sup>11</sup> A 2015 *Cochrane Systematic Review* evaluated the use of honey for the treatment of acute and chronic wounds. The authors looked at 25 qualifying randomized controlled trials totaling almost 3,000 patients and found honey to modestly reduce healing time for partial thickness burns but insufficient evidence to recommend its

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use in all other types of wounds including diabetic foot ulcers.<sup>24</sup>

A 2014 systematic review and meta-analysis published in *American Family Physicians* noted that while medical-grade topical honey can be used to reduce healing time in partial thickness burns, it produced no effect on lacerations, surgical wounds, chronic wounds, or vascular ulcers.<sup>21</sup>

Honey can potentially be an effective dressing in diabetic ulcers, as it covers against a wide range of bacteria and poses minimal risks. There are no reports of bacterial resistance to honey.<sup>16</sup> Honey's anti-inflammatory and de-sloughing properties also add to its benefits. However, similar to silver dressings, more high level, prospective randomized control trials are needed to delineate its effectiveness in comparison to other dressings.

## Polyhexamethylene Biguanide

Polyhexamethylene biguanide (PHMB) is an antiseptic agent that has been used as swimming pool sanitizers, preservatives in contact lens solutions, and wound irrigation fluid in Europe for well over 60 years.<sup>25,27</sup> It's a fast-acting compound similar to antimicrobial peptides (AMPs).<sup>25,26</sup> AMPs are produced within the wound by cells such as keratinocytes, and inflammatory neutrophils to protect the wound against invading organisms such as bacteria, fungus, and virus.<sup>25,26</sup> PHMB's structural similarity to AMP allows it to infiltrate bacterial cell membranes and kill bacteria in a similar fashion.<sup>25,26</sup> It causes target cell membranes to leak potassium and other dissolved ions from the cytoplasm, leading to cell death.<sup>25</sup>

PHMB affects the bacterial efflux pump, thereby disabling bacteria's ability to remove the antiseptic and maintaining intracellular concentrations.<sup>26</sup> Moreover, PHMB binds to DNA and other nucleic acids to damage or inactivate bacterial DNA.<sup>24</sup> PHMB, however, cannot enter the human nucleus, thereby protecting human DNA from damage.<sup>25,26</sup> It has been found safe in clinical use as it has minimal toxicity with no evidence of bacterial resistance.<sup>25,27</sup> In a large study involving a total of 3,529 sub-

jects, skin sensitization to PHMB was found to be approximately 0.5% even when the tested concentrations of 2.5% and 5% were five to ten times the concentration normally used in wound applications.<sup>25</sup> A 2016 systematic review only found six qualifying studies regarding PHMB in the literatures. While the authors were unable to conduct a meta-analysis due to the variability in methodology and outcome measures, existing evidence showed that topical PHMB may promote the healing of chronic stalled wounds, reduce bacterial burden, eliminate MRSA, and alleviate wound-related pain.<sup>28</sup>

## Conclusion

In summary, diabetic foot ulcers are a major problem present in the United States and across the globe. Choice of wound dressing products is of importance with respect to patient outcomes surrounding diabetic foot ulcers. Various agents have been applied topically to treat wounds for millennia but their proper role remains unclear. Topical therapies afford many potential advantages and disadvantages and current meta-analyses and systematic reviews suggest few proven indications for topical antimicrobials. At present, more randomized control studies are needed to effectively analyze and compare topical antimicrobial use in diabetic wound healing to aid in clinical decision-making and improving patient care and outcome. **PM**

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