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# Topical antimicrobial agents for treating foot ulcers in people with diabetes

Review

Intervention

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## Abstract

English

### Background

People with diabetes are at high risk for developing foot ulcers, which often become infected. These wounds, especially when infected, cause substantial morbidity. Wound treatments should aim to alleviate symptoms, promote healing, and avoid adverse outcomes, especially lower extremity amputation. Topical antimicrobial therapy has been used on diabetic foot ulcers, either as a treatment for clinically infected wounds, or to prevent infection in clinically uninfected wounds.

### Objectives

To evaluate the effects of treatment with topical antimicrobial agents on: the resolution of signs and symptoms of infection; the healing of infected diabetic foot ulcers; and preventing infection and improving healing in clinically uninfected diabetic foot ulcers.

## Search methods

We searched the Cochrane Wounds Specialised Register, CENTRAL, Ovid MEDLINE, Ovid MEDLINE (In-Process & Other Non-Indexed Citations), Ovid Embase, and EBSCO CINAHL Plus in August 2016. We also searched clinical trials registries for ongoing and unpublished studies, and checked reference lists to identify additional studies. We used no restrictions with respect to language, date of publication, or study setting.

## Selection criteria

We included randomised controlled trials conducted in any setting (inpatient or outpatient) that evaluated topical treatment with any type of solid or liquid (e.g., cream, gel, ointment) antimicrobial agent, including antiseptics, antibiotics, and antimicrobial dressings, in people with diabetes mellitus who were diagnosed with an ulcer or open wound of the foot, whether clinically infected or uninfected.

## Data collection and analysis

Two review authors independently performed study selection, 'Risk of bias' assessment, and data extraction. Initial disagreements were resolved by discussion, or by including a third review author when necessary.

## Main results

We found 22 trials that met our inclusion criteria with a total of over 2310 participants (one study did not report number of participants). The included studies mostly had small numbers of participants (from 4 to 317) and relatively short follow-up periods (4 to 24 weeks). At baseline, six trials included only people with ulcers that were clinically infected; one trial included people with both infected and uninfected ulcers; two trials included people with non-infected ulcers; and the remaining 13 studies did not report infection status.

Included studies employed various topical antimicrobial treatments, including antimicrobial dressings (e.g. silver, iodides), super-oxidised aqueous solutions, zinc hyaluronate, silver sulphadiazine, tretinoin, pexiganan cream, and chloramine. We performed the following five comparisons based on the included studies:

**Antimicrobial dressings compared with non-antimicrobial dressings:** Pooled data from five trials with a total of 945 participants suggest (based on the average treatment effect from a random-effects model) that more wounds may heal when treated with an antimicrobial dressing than with a non-antimicrobial dressing: risk ratio (RR) 1.28, 95% confidence interval (CI) 1.12 to 1.45. These results correspond to an additional 119 healing events in the antimicrobial-dressing arm per 1000 participants (95% CI 51 to 191 more). We consider this low-certainty evidence (downgraded twice due to risk of bias). The evidence on adverse events or other outcomes was uncertain (very low-certainty evidence, frequently downgraded due to risk of bias and imprecision).

**Antimicrobial topical treatments (non dressings) compared with non-antimicrobial topical treatments (non dressings):** There were four trials with a total of 132 participants

in this comparison that contributed variously to the estimates of outcome data. Evidence was generally of low or very low certainty, and the 95% CIs spanned benefit and harm: proportion of wounds healed RR 2.82 (95% CI 0.56 to 14.23; 112 participants; 3 trials; very low-certainty evidence); achieving resolution of infection RR 1.16 (95% CI 0.54 to 2.51; 40 participants; 1 trial; low-certainty evidence); undergoing surgical resection RR 1.67 (95% CI 0.47 to 5.90; 40 participants; 1 trial; low-certainty evidence); and sustaining an adverse event (no events in either arm; 81 participants; 2 trials; very low-certainty evidence).

**Comparison of different topical antimicrobial treatments:** We included eight studies with a total of 250 participants, but all of the comparisons were different and no data could be appropriately pooled. Reported outcome data were limited and we are uncertain about the relative effects of antimicrobial topical agents for each of our review outcomes for this comparison, that is wound healing, resolution of infection, surgical resection, and adverse events (all very low-certainty evidence).

**Topical antimicrobials compared with systemic antibiotics :** We included four studies with a total of 937 participants. These studies reported no wound-healing data, and the evidence was uncertain for the relative effects on resolution of infection in infected ulcers and surgical resection (very low certainty). On average, there is probably little difference in the risk of adverse events between the compared topical antimicrobial and systemic antibiotics treatments: RR 0.91 (95% CI 0.78 to 1.06; moderate-certainty evidence - downgraded once for inconsistency).

**Topical antimicrobial agents compared with growth factor:** We included one study with 40 participants. The only review-relevant outcome reported was number of ulcers healed, and these data were uncertain (very low-certainty evidence).

## Authors' conclusions

The randomised controlled trial data on the effectiveness and safety of topical antimicrobial treatments for diabetic foot ulcers is limited by the availability of relatively few, mostly small, and often poorly designed trials. Based on our systematic review and analysis of the literature, we suggest that: 1) use of an antimicrobial dressing instead of a non-antimicrobial dressing may increase the number of diabetic foot ulcers healed over a medium-term follow-up period (low-certainty evidence); and 2) there is probably little difference in the risk of adverse events related to treatment between systemic antibiotics and topical antimicrobial treatments based on the available studies (moderate-certainty evidence). For each of the other outcomes we examined there were either no reported data or the available data left us uncertain as to whether or not there were any differences between the compared treatments. Given the high, and increasing, frequency of diabetic foot wounds, we encourage investigators to undertake properly designed randomised controlled trials in this area to evaluate the effects of topical antimicrobial treatments for both the prevention and the treatment of infection in these wounds and ultimately the effects on wound healing.

## Plain language summary

English

### Topical antimicrobial agents (antibacterial products applied directly to wounds) for treating foot ulcers in people with diabetes

#### Review question

We reviewed the evidence about whether or not antimicrobial agents (antibacterial products) can prevent or treat foot infections in people with diabetes when they are applied topically (directly to the affected area). We wanted to find out if antibacterial treatments could help both infected and uninfected wounds to heal, and prevent infection in uninfected wounds.

#### Background

People with diabetes are at high risk of developing foot ulcers. These wounds can cause discomfort and often become infected. Diabetic foot ulcers that do not heal can result in amputation of part or all of the foot or even the lower leg. Antimicrobial agents, such as antiseptics and antibiotics, kill or prevent bacteria from growing, and are sometimes used to treat diabetic foot ulcers. Antimicrobials may be used either to reduce infection or promote healing in infected wounds, or to prevent infection or promote healing in wounds where infection has not been detected. We wanted to find out whether antimicrobial treatments were effective in either of these cases; which treatments were most effective; and if those treated experienced any harmful side effects.

#### Study characteristics

In August 2016 we searched for randomised controlled trials involving the use of any antimicrobial treatment on foot ulcers or other open wounds of the foot in people with diabetes. We found 22 trials involving a total of over 2310 adult participants (one trial did not report the number of participants). Participant numbers in each trial ranged from 4 to 317 and follow-up times during and after treatment ranged from 4 to 24 weeks. Some trials included participants with ulcers that were infected, while other trials included participants with ulcers that were uninfected. The trials compared a variety of different antimicrobial dressings, solutions, gels, creams, or ointments.

#### Key results

Many of the trials did not report important data, which means the reliability of the results is uncertain. The results of five trials involving 945 participants suggest that use of some type of antimicrobial dressing may increase the number of ulcers healed in medium-term follow-up (4 to 24 weeks) when compared with a non-antimicrobial dressing (low certainty evidence). Due to limited information, we were unable to assess the effectiveness of treatments in either preventing or resolving wound infection. Four trials involving 937 participants compared systemic antibiotics (given by mouth or via injection, distributed to the whole body by the bloodstream) with antimicrobial treatments applied directly to the wound. These trials did not provide data on healing or infection, but it appeared that there was no difference in the side effects experienced by participants whose ulcers were treated systemically or topically (moderate certainty evidence).

#### Quality of the evidence

Overall, the certainty of the evidence provided by the trials was too low for us to be certain of the benefits and harms of topical antimicrobial treatments for treating foot ulcers in people with diabetes. More, larger, and better-designed randomised controlled trials should be carried out in this area.

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