A systematic review of foot ulcer in patients with Type 2 diabetes mellitus - II: treatment

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Authors' objectives
To assess the value of treatments for foot ulcers in patients with Type 2 diabetes mellitus.

Searching
The following databases were searched: Cochrane Controlled Trials Register, MEDLINE, EMBASE, CINAHL, HealthSTAR, PsycLIT, Science Citation Index and Social Sciences Citation Index. All databases were searched from 1983 onwards. The search strategy used was reported to have been an optimally sensitive one using both subject headings and textwords. Trial registers were searched for ongoing and unpublished trials, and conference proceedings were examined using the Index to Scientific and Technical Conference Proceedings (ISTP). Attempts to access 'grey literature' were made using the HIMC database (which includes the catalogues of the King's Fund, the Nuffield Institute and the Department of Health libraries) and SIGLE.

Study selection
Study designs of evaluations included in the review
In each area, the best evidence available was reported to have been used (see Other Publications of Related Interest no.1). Where randomised controlled trials (RCTs) were available, studies of lesser design were excluded, unless they added a further dimension to the understanding. Unpublished manuscripts not awaiting publication were excluded.

Specific interventions included in the review
Any intervention used to treat diabetic foot ulcers. The review did not include vascular surgical techniques, the appropriate method or timing of amputations or subsequent management. The types of interventions evaluated by included studies were: antibiotic therapy, dressings and topical agents, cultured human dermis, casting, hyperbaric oxygen therapy, ketanserin, growth factors, granulocyte-colony stimulating factor and education of patients with foot ulcers. Control therapy included: placebo, alternative antibiotic therapy, gauze moistened in saline, dry sterile gauze or alternative modern dressing, conventional or usual care.

Participants included in the review
Patients with Type 2 diabetes who have diabetic foot ulcers. Studies that addressed Type 1 as well as Type 2 diabetes were included. Studies that only included participants with Type 1 diabetes were excluded. The review did not address specific treatments for neuropathy, peripheral vascular disease or charcot foot.

Outcomes assessed in the review
No a-priori outcome measures were reported. Specific outcomes used by included studies were: lesions completely closed or healed, reduction in ulcer radius, lesions improved, cured or healing in progress, infection response (cured, improved or failed), side-effects/adverse effects, number of withdrawals, surgery, amputation, mortality, clinically relevant improvement, weekly cost, percentage reduction in wound area, time required for 50% wound healing, ulcers assessed on clinical impression scale on day 35, time to complete healing, wound size at specific time, infection requiring hospitalisation, change in ulcer depth, transcutaneous oxygen tension, gangrene, volume reduction, time to hospital discharge, time to resolution of cellulitis, time to cessation of antibiotics, time to negative swab culture, cellulitis resolved at 7 days.

How were decisions on the relevance of primary studies made?
Assessment of papers retrieved was conducted independently by two of the authors and disagreements were resolved by discussion.

Assessment of study quality
The validity criteria used to assess studies included, level of blinding, concealment of allocation, baseline comparability,
numbers randomised (or numbers included for non-RCTs) and loss to follow-up. The validity assessment appears to have been undertaken at the same time as data extraction that was conducted independently by two of the authors and disagreements were resolved by discussion.

Data extraction
Data extraction was conducted independently by two of the authors and disagreements were resolved by discussion. The categories of data extraction used included: reference details, intervention, trial detail (validity assessment) and results.

Methods of synthesis
How were the studies combined?
Studies were combined in a narrative using, where appropriate, meta-analytical techniques. A random-effects model was used to combine studies looking at cultured human dermis.

How were differences between studies investigated?
Heterogeneity between some included studies was discussed in a narrative.

Results of the review
Twenty-nine RCTs were included in the review. For the evaluation of antibiotic therapy, four RCTs (n=301) were included. Eight RCTs (n=446) and two non-randomised prospective controlled studies (n=140) evaluated dressings and topical agents and two RCTs (n=331) investigated the use of cultured human dermis. There was also one RCT (n=40) of casting, two RCTs (n=98) of hyperbaric oxygen therapy, two RCTs (n=201) of ketanserin, six RCTs (n=664) of growth factors, one RCT (n=40) of granulocyte-colony stimulating factor and one RCT (n=203) that investigated the use of education for patients with foot ulcers.

Antibiotic therapy (4 RCTs):
Two trials addressed non-limb threatening infection, one addressed non-limb threatening, though treatment-resistant, infection, one addressed invasive infection.

The two outpatient trials of noninvasive infections found no difference between antibiotic regimens and no improvement relative to placebo. It is uncertain whether all antibiotics are ineffective in this group of patients or just the particular regimen used. The remaining two trials also found no significant difference between the treatment groups in clinical response. Despite the apparent treatment success reported by one trial (after 5 days, cure had been effected in 60% of the ampicillin/sulbactam group and 58% of the imipenem/cilastin group), 66% of their patients had a lower limb amputation during the following year, although the operation was limb sparing in most cases.

Dressings and topical agents for foot ulcers (8 RCTs and 2 controlled trials):
Trials were broadly grouped into those comparing newer dressings or gels (alginate, foam, hydrogel and hydrocolloid dressings) with gauze dressings (6 RCTs and two controlled trials) and those comparing the newer dressings with one another (2 RCTs).

For the comparison of newer dressings with gauze, although some findings appeared promising, neither a positive or negative finding could be regarded as conclusive when based on one small trial. The stated importance of the newer dressings and the inappropriateness of gauze do not appear substantiated by the limited evidence from RCTs. The two head-to-head trials comparing newer dressing technologies suggested broad equivalence but no firm conclusions could be drawn from these small unreplicated studies.

Cultured human dermis (2 industry-sponsored RCTs):
Although concerns about the trial estimates remain, a meta-analysis of trial results in terms of risk difference was conducted. Weekly Dermagraft is estimated to result in a non-significant 21% increase in ulcers healing at 12 weeks (95% CI: -13 to 56%) compared to control group.
Casting (1 RCT):

The absolute risk reduction for complete skin closure with no drainage was 58.9% (95% CI: 30.3 to 78.3%) in favour of total contact casting. Mean time to ulcer healing and infections requiring hospitalisation also significantly favoured total contact casting (TCC).

Hyperbaric oxygen (2 RCTs):

One trial reported that ulcers in both groups improved significantly, but there was no significant difference between the groups at 2 weeks follow-up. One trial reported that major amputation was significantly lower in the treated group (8.6%) than the control group (33.0%) p=0.016). There were no significant differences in minor amputations. The two trials were reported to have had a number of differences that may explain their conflicting results which included severity of ulcers being investigated and the type of oxygen therapy used (topical versus inhaled, and the use of substantially raised or sustained pressure as opposed to not).

Ketanserin (2 RCTs):

These trials report different end points, making comparison between studies problematic. The respective bioavailabilities of topical or oral ketanserin are not clear. One trial that was considered to be relatively large implied a clinically important benefit from topically applied ketanserin when used in addition to comprehensive care in relatively severe ulcers.

Growth factors (6 RCTs):

Four types of growth factor (GF) were evaluated by included trials (CT-102 which is derived from a thrombin-induced human platelet process (2 RCTs); rhPDGF which is a recombinant platelet derived GF (2 RCTs); rbFGF which is a recombinant basic fibroblast GF using Escherichia coli type beta (1 RCT); and RGDpm which is an arginine-glycine-aspartic acid peptide matrix (1RCT)).

The available trials of GFs suggest potentially important benefits from three applied GF in addition to conventional care: CT-102 (dilution 0.01), RGDpm and rhPDGF. On the basis of one small pilot study, there is no evidence for the use of rbFGF. When reported, GFs appear well tolerated, with no drug-related side-effects.

Granulocyte-colony stimulating factor (1 RCT):

There was a statistically significant reduction in median time to hospital discharge, resolution of cellulitis, withdrawal of intravenous antibiotics and negative swab culture for patients receiving G-CSF. At day 7, cellulitis had resolved in 55% of patients on G-CSF and 20% on placebo (P=0.05), and healing had occurred in 21% of patients on G-CSF and 0% on placebo (P=0.09).

Education of patients with foot ulcers (1 RCT):

The study showed a reduction in the combined end point of limbs free of infection, ulcer or amputation, favouring education (education 90%, control 72%). Although there were no significant difference in infection or mortality during follow-up, there was an excess of ulceration (education 5%, control 15%) and amputation (education 4%, control 12%) in the control group. Statistical calculations assumed ‘independence’ of limbs which may have resulted in over-precision.

Cost information

There was some cost information presented relating to granulocyte-colony stimulating factor. Filgrastim is expensive. Using the median reported dose, seven days of treatment in British primary care costs approximately £540 to purchase per patient.

Authors' conclusions

Available trials of antibiotics for infected foot ulcers are uninformative. No robust evidence of the relative
effectiveness or cost-effectiveness of any dressing has emerged, despite the received wisdom regarding newer dressing types. The role of cultured human dermis, G-CSF, growth factors, HBO therapy, ketanserin, and TCC can neither be ruled in nor out on the basis of available evidence, although some of these technologies show considerable promise. Caution is appropriate, since the medical literature contains many examples of auspicious early findings from trials refuted by definitive studies.

**CRD commentary**

This was a fairly well conducted review. The aims were clearly stated and a comprehensive literature search was undertaken which included a search of the ‘grey literature’. Unpublished manuscripts not awaiting publication were excluded, the extent of which was not reported, and it is therefore not known if important information may have been left out. A systematic procedure involving one or more reviewers was used to assess the relevancy of retrieved articles and data extraction. The authors also assessed the validity of included trials. Relevant details of included RCTs were clearly presented in tables and described in the text. Differences between included studies were briefly discussed and a narrative synthesis of the results was appropriate. The overall findings for each section were not always clearly presented. However, the authors' conclusions follow from the results, which took into consideration the poor quality of the included studies.

**Implications of the review for practice and research**

*Practice:* The authors do not report any implications for practice.

*Research:* The authors note that the findings of included trials assessing the efficacy of antibiotic therapy in diabetic patients with infected foot ulcers need confirmation from further well-conducted studies using common methods and end points. They also note that the use of casting techniques in the treatment of diabetic foot ulcers requires further investigation, as does hyperbaric oxygen therapy and topically applied ketanserin (when used in addition to comprehensive care) for the treatment of relatively severe ulcers. The results relating to growth factors, granulocyte-colony stimulating factors and education of patients with foot ulcers were also reported to need confirmation from further trials. It was noted that future trials of newer interventions should also include an assessment of cost-effectiveness.

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**Other publications of related interest**


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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.