A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers


CRD summary
This review assessed the performance and effectiveness of methods to diagnosis, manage and treat infected diabetic foot ulcers. This well-conducted review reliably concluded that there was insufficient evidence on which to base any conclusions. Recommendations for further research were proposed.

Authors’ objectives
To review the performance and effectiveness of methods for the diagnosis, management and treatment of infected diabetic foot ulcers.

Searching
Nineteen electronic databases including MEDLINE, PREMEDLINE, EMBASE, AMED, British Nursing Index and CINAHL were searched from inception to November 2002. In addition, two internet registers of ongoing research (Controlled Clinical Trials and the National Research Register), nine internet sources for clinical guidelines or reviews, six conference proceedings, one journal (The Diabetic Foot) and three books were searched for additional studies. No language restrictions were applied. Details of the full search strategy including search terms were reported.

Study selection
Study designs of evaluations included in the review
Any comparative study design was eligible for inclusion in the review of diagnostic and sampling methods if sufficient data were reported for the construction of a 2x2 diagnostic table (i.e. the number of true positives, false positives, true negatives and false negatives).

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were eligible for inclusion in the review of treatment effectiveness and the review of the impact of microbiological analysis on therapy or outcomes.

Specific interventions included in the review
The review of diagnostic methods included studies assessing clinical examination, any method for microbiological sample acquisition and any method for analysing microbiological samples. Studies included in the review assessed: clinical examination based on 11 signs and symptoms (increasing pain; erythema; oedema; heat; purulent exudates; serous exudates plus concurrent inflammation; delayed healing; discoloration; friable granulation; foul odour; and wound breakdown); wound swabbing with microbiological counts using a quantitative analysis; and microbiological counts using a semi-quantitative analysis. Studies assessing diagnostic methods for osteomyelitis and other problems associated with foot infection not involving ulceration were not included in the review.

The review of treatments included studies assessing antimicrobial agents delivered in any setting compared with placebo, no intervention, or standard care. Studies were excluded if they used any concurrent intervention which may influence healing, such as pressure relief, optimisation of blood glucose control and improvement of blood supply to the foot. The interventions assessed in the review included oral, intravenous, subcutaneous, topical and other types of antimicrobial agents. The treatments were compared with each other or with standard care. Further details of the included interventions and treatment regimens were reported.

Eligible studies for inclusion in the review of impact of microbiological analysis on therapy or outcomes had to compare relevant strategies or policies of prescribing antimicrobial agents in any health care setting.

Reference standard test against which the new test was compared
Diagnostic and sampling methods compared with any independent reference standard were eligible for inclusion. The
studies included in the review used punch biopsy or quantitative microbiological counts as the reference standard.

Participants included in the review
Studies of adult patients (at least 18 years old) with infected diabetic foot ulcers were eligible for inclusion. Studies of patients with purely infected foot ulcers or osteomyelitis without ulceration were excluded from the review. The populations of patients were often mixed and a post hoc decision was made to include studies if at least 80% of the patients had diabetic foot ulcer. However, patients with diabetic foot ulcers constituted a minority of the total study population in all of the included diagnostic studies and the data were not presented separately for those with diabetic foot ulcer and other patients. Further details of the patient characteristics were reported.

Outcomes assessed in the review
Diagnostic and sampling studies assessing sensitivity and specificity were eligible for inclusion in the review.

Treatment studies and studies of the impact of microbiological analysis on therapy or outcomes, that reported at least one outcome measure relating to mortality, amputation, wound healing, infection profile, mobility/function, quality of life or changes in ulcer characteristics, were eligible for inclusion in the review.

Adverse events and adherence to treatment were also included. Further details of the eligible outcome measures were reported.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed both titles and abstracts and full papers. Any disagreements were resolved through discussion.

Assessment of study quality
Two reviewers independently assessed the validity of the included studies; any disagreements were resolved through discussion.

Diagnostic and sampling studies were assessed using the 12-item Quality Assessment of Diagnostic Accuracy Studies Assessment (QUADAS) tool; criteria were rated as 'yes', 'no' or 'unclear'.

Effectiveness studies were assessed using the Jadad scale (randomisation, double-blinding and withdrawals) and the allocation concealment criterion described by Schultz. The studies were awarded a score from 0 to 5 points on the Jadad scale and were graded A (adequate), B (unclear) or C (inadequate) for the Schultz criterion. In addition, the following criteria were added to the assessment of CCTs: the method of allocation, the degree of baseline comparability and the consideration of baseline differences in the analysis.

Data extraction
One reviewer extracted the data using a structured extraction table and a second reviewer independently checked these data. Any disagreements were resolved through discussion. Authors were contacted for missing data.

The percentage sensitivity and specificity were recorded for diagnostic and sampling studies, along with reference data and any definitions of infection such as the number of colony-forming units per amount of tissue or culture. For studies of effectiveness, relative risks with 95% confidence intervals were reported for dichotomous outcomes and mean differences with 95% confidence intervals for continuous outcomes.

Methods of synthesis
How were the studies combined?
The diagnostic and sampling studies were discussed individually using a narrative summary.

Effect sizes for treatment intervention studies were pooled using a random-effects model where appropriate or otherwise synthesised in narrative summary. Pooled relative risks were calculated where event rates were over 30% and pooled odds ratios where event rates were below 30%.
How were differences between studies investigated?
Differences between the studies were evident from the data tables and were discussed within the text of the review. Statistical heterogeneity was assessed, where appropriate, using the chi-squared test. Studies of treatment effectiveness were grouped according to the type of intervention (i.e. intravenous, oral, subcutaneous, topical and other interventions).

Results of the review
The review of diagnostic and sampling methods included 3 studies (n=198), two of which were cross-sectional studies. However, only 41 participants had wounds associated with diabetes.

The review of treatment interventions included 23 studies (total number of participants was unclear): 21 RCTs and 2 CCTs. No studies were identified for the review of the impact of microbiological analysis on therapy or outcomes.

Diagnostic and sampling methods.
All 3 studies failed to report whether the test results were interpreted blindly and whether an appropriate reference standard was used. It was also unclear whether the interpretation of the test results considered data that would be available in clinical practice.

One cross-sectional study (n=36) comparing a checklist of 11 clinical signs and symptoms with punch biopsy (reference standard) suggested that none of the signs or symptoms were useful as a diagnostic test. The sensitivity of items ranged from 18 to 82%; the specificities ranged from 64 to 100%. Only two of the participants had diabetic foot ulcers.

One cross-sectional study (n=38) comparing wound swabs with quantitative analysis with punch biopsy (reference standard) suggested that wound swabbing (sensitivity 79%; specificity 60%) was not a useful diagnostic test. Only 10 of the participants had diabetes and foot ulceration.

One study (n=124) comparing semi-quantitative analysis of wound swabs with quantitative analysis (reference standard) suggested that a threshold of three or four quadrants on an agar plate was the most useful threshold for this test (sensitivity 79%; specificity 90%). However, this would produce a false-negative rate of 21% in practice, which would result in patients receiving delayed treatment. Only 29 patients had neuropathic ulcers or ulcers due to diabetes.

Treatment effectiveness.
Nine studies reported adequate methods of randomisation; two reported adequate methods of allocation concealment; three described appropriate double-blinding; and 13 studies reported the number and reason for withdrawals. Study methods were often poorly reported making quality assessment difficult. Two RCTs were reported as good quality but were underpowered due to small sample sizes.

Intravenous interventions (6 RCTs and 2 CCTs): no robust evidence of the superiority of one intervention over another was found. One RCT reported that cefoxitin was better than ampicillin and sublactam in terms of clinical cure, but differences in amputation, revascularisation, bacterial eradication or adverse effects were not reported. Another RCT reported that imipenem and cilastatin were associated with fewer adverse events than piperacillin and clindamycin, but differences in bacterial eradication or clinical cure were not reported. One RCT reported that the length of treatment with ampicillin and sulbactam or amoxycillin and clavulanate was greater than with linezolid, but differences in clinical cure and adverse events were not reported.

Oral interventions (5 RCTs): no robust evidence of the superiority of one intervention over another was found. One study compared oral antibiotics with placebo; two compared alternative oral antimicrobial agents; and two compared oral and topical interventions. No significant differences in any of the outcomes were reported, although 3 trials were reported to be underpowered.

Subcutaneous interventions (4 RCTs): no robust evidence of the superiority of granulocyte-colony stimulating factor (G-CSF) was found either alone or in combination with standard care, when compared with placebo and standard care, or standard care alone. However, the trials were all small in size and underpowered. No studies compared subcutaneous
interventions with intravenous, oral or tropical treatments.

Topical interventions (5 RCTs): no robust evidence of the superiority of one intervention over another was found in any of the eight comparisons. One RCT reported more ulcer healing with a hydrogel than a topical chlorhexidine gauze, but this study suffered from methodological limitations.

Other interventions (1 RCT): one RCT compared topical and oral formulations of a decoction of plant extracts. However, the data were poorly reported, adverse effects were not reported, and the trial was underpowered.

Cost information
The authors also carried out a systematic review of cost-effectiveness studies. Two studies assessed the cost-effectiveness of antimicrobial agents for the treatment of infected diabetic foot ulcers. The studies suggested that both G-CSF and cadexomer iodine dressings may be less expensive than 'standard care', and that ampicillin and sulbactam may be less costly than imipenem and cilastatin. The authors also carried out their own decision analytic modelling to investigate the cost-effectiveness of different combinations of interventions and diagnostic tests.

Authors' conclusions
The available evidence was too weak to draw any conclusions about the optimal methods for diagnosing or treating infection in patients with diabetic foot ulcers. Recommendations for further research are given.

CRD commentary
This was a well-conducted and clearly reported review based on appropriately defined inclusion criteria. The authors took appropriate steps to locate both published and unpublished studies in all languages, thereby minimising the risk of publication and language bias. Details of the review process were reported clearly and steps were taken to minimise bias and error. Differences between the studies often precluded the authors’ planned meta-analysis and, instead, a narrative summary was appropriately used to summarise the study data. Where pooling was appropriate, statistical and clinical heterogeneity was considered. Given the data presented, the authors were justified in not drawing any conclusions from their review. Their recommendations for further research appear reasonable.

Implications of the review for practice and research
Practice: The authors reported that the available evidence was too weak to make recommendations for practice.

Research: The authors stated that further rigorous research using adequate sample sizes and reported according to CONSORT (Consolidated Standards of Reporting Trials) and STARD (Standards for Reporting of Diagnostic Accuracy) guidelines is required. Future studies should assess the diagnostic performance of clusters of clinical signs and symptoms, and evaluate the adverse effects of diagnostic tests and their impact on patient outcomes. Optimum reference standards need to be established. Studies comparing different treatments are also required, e.g. combinations of broad-spectrum antibiotics, larval therapy, growth factors and topical agents or dressings.

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