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

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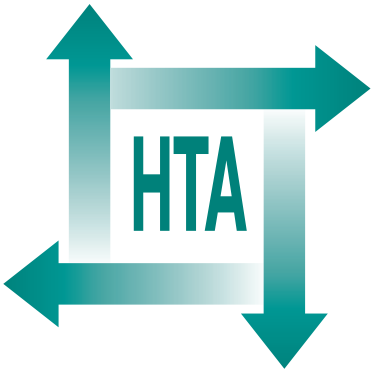

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The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

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The research reported in this monograph was commissioned by the HTA Programme as project number 01/05/02. The contractual start date was in July 2002. The draft report began editorial review in June 2004 and was accepted for publication in August 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

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

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Objectives: To review systematically the evidence on the performance of diagnostic tests used to identify infection in diabetic foot ulcers (DFUs) and of interventions to treat infected DFUs. To use estimates derived from the systematic reviews to create a decision analytic model in order to identify the most effective method of diagnosing and treating infection and to identify areas of research that would lead to large reductions in clinical uncertainty.
Data sources: Electronic databases covering period from inception of the database to November 2002.
Review methods: Selected studies were assessed against validated criteria and described in a narrative review. The structure of a decision analytic model was derived for two groups of patients in whom diagnostic tests were likely to be used.
Results: Three studies that investigated the performance of diagnostic tests for infection on populations including people with DFUs found that there was no evidence that single items on a clinical examination checklist were reliable in identifying infection in DFUs, that wound swabs perform poorly against wound biopsies, and that semi-quantitative analysis of wound swabs may be a useful alternative to quantitative analysis. However, few people with DFUs were included, so it was not possible to tell whether diagnostic performance differs for DFUs relative to wounds of other aetiologies. Twenty-three studies investigated the effectiveness ($n = 23$) or cost-effectiveness ($n = 2$) of antimicrobial agents for DFUs. Eight studied intravenous antibiotics, five oral antibiotics, four different topical agents such as dressings, four subcutaneous granulocyte colony stimulating factor (G-CSF), one evaluated oral and topical Ayurvedic preparations and one compared topical sugar versus antibiotics versus standard care. The majority of trials were underpowered and were too dissimilar to be pooled. There was no strong evidence for recommending any particular antimicrobial agent for the prevention of amputation, resolution of infection or ulcer healing. Topical pexiganan cream may be as effective as oral antibiotic treatment with ofloxacin for the resolution of local infection. Ampicillin and sulbactam were less costly than imipenem and cilastatin, a growth factor (G-CSF) was less costly than standard care and cadexomer iodine dressings may be less costly than daily dressings. A decision analytic model was derived for two groups of people, those for whom diagnostic testing would inform treatment – people with ulcers which do not appear infected but whose ulcer is not progressing despite optimal concurrent treatment – and those in whom a first course of antibiotics (prescribed empirically) have failed. There was insufficient information from the systematic reviews or interviews with experts to populate the model with transition probabilities for the sensitivity and specificity of diagnosis of infection in DFUs. Similarly, there was insufficient information on the probabilities of healing, amputation or death in the intervention studies for the two populations of interest.

Therefore, we were unable to run the model to inform the most effective diagnostic and treatment strategy.

Conclusions: The available evidence is too weak to be able to draw reliable implications for practice. This means that, in terms of diagnosis, infection in DFUs cannot be reliably identified using clinical assessment. This has implications for determining which patients need formal diagnostic testing for infection, on whether empirical treatment with antibiotics (before the results of diagnostic tests are available) leads to better outcomes, and on identifying the optimal methods of diagnostic testing. With respect to treatment, it is not known whether treatment with systemic or local antibiotics leads to better outcomes or whether any particular agent is more effective. Limited evidence suggests that both G-CSF and cadexomer iodine dressings may be less expensive than 'standard' care, that ampicillin/sulbactam may be less costly than imipenem/cilastatin, and that an unlicensed cream (pexiganan) may be as effective as oral ofloxacin. Further research is needed to ascertain the characteristics of infection in people with DFUs that influence healing and amputation outcomes, to determine whether detecting infection prior to treatment offers any benefit over empirical therapy, and to establish the most effective and cost-effective methods for detecting infection, as well as the relative effectiveness and cost-effectiveness of antimicrobial interventions for DFU infection.

Contents

List of abbreviations

A/C	amoxycilin and clavulanate
A/S	ampicillin and sulbactam
CCT	controlled clinical trial
CFU	colony-forming unit
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRD	Centre for Reviews and Dissemination
DFU	diabetic foot ulcer
DNA	deoxyribonucleic acid
DNPU	diabetic neuropathic plantar ulcer
DPN	diabetic peripheral neuropathy
EQ-5D	EuroQol quality of life questionnaire
G-CSF	granulocyte colony-stimulating factor
HEED	Health Economics Evaluation Database
HRQoL	health-related quality of life
I/C	imipenem and cilastatin
LR	likelihood ratio
+LR	positive likelihood ratio
–LR	negative likelihood ratio
MRSA	methicillin-resistant *Staphylococcus aureus*
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NPV	negative predictive value
P/C	piperacillin and clindamycin
P/T	piperacillin and tazabacam
PCR	polymerase chain reaction
PPV	positive predictive value
QALY	quality-adjusted life-year
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews
QUOROM	Quality of Reporting of Meta-Analyses
RCT	randomised controlled trial
rh-G-CSF	recombinant human granulocyte colony-stimulating factor
rhPDGF	recombinant human platelet-derived growth factor
ROC	receiver operating characteristic
RR	relative risk
RVP	retrograde venous perfusion
SD	standard deviation
SEK	Swedish kroner
SPSS	Statistics Package for Social Sciences
STARD	Standards for Reporting of Diagnostic Accuracy
T/C	ticarcillin and clavulanate
VAS	visual analogue scale

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Around 6% of people with diabetes have a foot ulcer or have a history of one. Diabetic foot ulcers (DFUs) are associated with increased mortality, illness and reduced quality of life. Diagnosing infection in DFU accurately and administering antibiotics may be important as infection can lead to amputation. However, using antimicrobial agents inappropriately could be costly, and lead to increased bacterial resistance. This review concentrates on the diagnosis of infection and the management of DFUs with antimicrobial agents.

Objectives

The objectives of this study were:

- To review systematically the evidence on the performance of diagnostic tests used to identify infection in DFUs and of interventions to treat infected DFUs.
- To use estimates derived from the systematic reviews to create a decision analytic model in order to identify the most effective method of diagnosing and treating infection and to identify areas of research that would lead to large reductions in clinical uncertainty.

Methods

Data sources

Electronic searches were made of 19 databases covering the period from inception of each database to November 2002. In addition, handsearches of book chapters, conference proceedings, a journal and bibliographies of retrieved studies were carried out. Internet searches were also made.

Study selection

Studies that dealt with the following areas were selected.

Diagnosis

Studies of the diagnosis of infection in people with DFUs or venous leg ulceration where a reference standard was compared with an alternative assessment.

Effectiveness

Randomised controlled trials (RCTs) or controlled clinical trials (CCTs) of the effect of microbiological analysis or antimicrobial agents in people with DFUs.

Cost-effectiveness

Economic evaluations of eligible interventions studied in which costs and effectiveness were synthesised.

Modelling

Economic or decision analytic models in which the progress of patients with DFUs was described in sufficient detail to allow replication of the model.

Data extraction

Quality checklists and data extraction forms for each study design were completed by one reviewer and checked by a second. Interviews were held with experts to inform gaps in the evidence.

Data synthesis

Studies were described in a narrative review. The structure of a decision analytic model was derived for two groups of patients in whom diagnostic tests were likely to be used.

Results

Diagnosis

Three studies investigated the performance of diagnostic tests for infection on populations including people with diabetic foot ulcers. One study investigated the performance of clinical assessment, another investigated the performance of punch biopsy versus wound swab and quantitative analysis and the third compared quantitative and semi-quantitative wound swabs in people with chronic wounds, including DFUs, for the identification of infection. These studies, all of which looked at identifying infection in chronic wounds, found that:

- There was no evidence that single items on a clinical examination checklist were reliable in identifying infection in DFUs.
- Wound swabs performed poorly against wound biopsies.

- Semi-quantitative analysis of wound swabs may be a useful alternative to quantitative analysis.

For the three diagnostic studies few people with DFUs were included, so it was not possible to tell whether diagnostic performance differs for DFUs relative to wounds of other aetiologies.

Effectiveness

Twenty-three studies investigated the effectiveness ($n = 23$) or cost-effectiveness ($n = 2$) of antimicrobial agents for DFU. Eight studied intravenous antibiotics, five oral antibiotics, four different topical agents such as dressings, four subcutaneous granulocyte colony stimulating factor (G-CSF), one evaluated oral and topical Ayurvedic preparations and one compared topical sugar versus antibiotics versus standard care.

The majority of trials were underpowered and were too dissimilar to be pooled. There was no strong evidence for recommending any particular antimicrobial agent for the prevention of amputation, resolution of infection or ulcer healing. Topical pexiganan cream may be as effective as oral antibiotic treatment with ofloxacin for the resolution of local infection.

Ampicillin and sulbactam were less costly than imipenem and cilastatin, a growth factor (G-CSF) was less costly than standard care and cadexomer iodine dressings may be less costly than daily dressings.

Decision analytic model

A decision analytic model was derived for two groups of people, those for whom diagnostic testing would inform treatment – people with ulcers which do not appear infected but whose ulcer is not progressing despite optimal concurrent treatment – and those in whom a first course of antibiotics (prescribed empirically) have failed. There was insufficient information from the systematic reviews or interviews with experts to populate the model with transition probabilities for the sensitivity and specificity of diagnosis of infection in DFUs. Similarly, there was insufficient information on the probabilities of healing, amputation or death in the intervention studies for the two populations of interest. Therefore, we were unable to run the model to inform the most effective diagnostic and treatment strategy.

Conclusions

Implications for healthcare

The available evidence was too weak to be able to draw reliable implications for practice. This means that, in terms of diagnosis, infection in DFUs cannot be reliably identified using clinical assessment. This also has implications for determining which patients need formal diagnostic testing for infection, whether empirical treatment with antibiotics (before the results of diagnostic tests are available) leads to better outcomes, and identifying the optimal methods of diagnostic testing. With respect to treatment, we do not know whether treatment with systemic or local antibiotics leads to better outcomes or whether any particular agent is more effective. Limited evidence suggests that both G-CSF and cadexomer iodine dressings may be less expensive than 'standard' care, that ampicillin/sulbactam may be less costly than imipenem/cilastatin, and also that an unlicensed cream (pexiganan) may be as effective as oral ofloxacin.

Implications for research

Questions to be answered are:

- What characteristics of infection in people with DFUs influence healing and amputation outcomes?
- Does detecting infection prior to treatment offer any benefit over empirical therapy?
- If detecting infection offers clinical benefit, then what are the most effective and cost-effective methods for detecting infection, e.g. clinical assessment, wound swabbing or wound biopsy and microbiological analysis, or novel techniques such as electronic nose/tongue and polymerase chain reaction analysis?
- What are the relative effectiveness and cost-effectiveness of antimicrobial interventions for DFU infection, e.g. combinations of broad-spectrum antibiotics, larval therapy, growth factors and topical agents/dressings?

Chapter 1
Background

The impact of diabetic foot ulcers

Diabetic foot ulcers (DFUs) are costly and associated with increased mortality, the development of morbidity and reduced quality of life. It has been estimated that the proportion of people with diabetes in the UK who have ever had foot ulceration is around 6%.[1] Currie and colleagues analysed routine inpatient data from a hospital in Cardiff, UK, and estimated that the cost per admission for DFU was £1451 and that the extrapolated annual national cost would be £17 million (price year 1994).[2] A prognostic study conducted in the USA showed that presence of foot ulceration was related to a higher risk of short-term mortality (mean follow-up 692 days) in people with diabetes.[3]

A large proportion of DFUs may fail to heal and are associated with the development of infection (including osteomyelitis) and/or gangrene and an increased risk of lower extremity amputation.[4,5] A review of European studies examining the incidence of amputations in diabetic patients reported estimates ranging from 5.7 to 20.5 amputations per 100,000 total population per year.[1] Although the variation in estimates may be due to differences between the characteristics of the various populations studied, it is also likely to be explained by differences in the ways in which amputation rates are recorded and expressed.[1]

Amputation can be performed at several different levels, including the following: toe excision; toe and ray excision (longitudinal amputation of a toe and its metatarsal); tarsometatarsal (Lisfranc) disarticulation (amputation of junction of tarsus and metatarsus); midtarsal (Chopart) disarticulation (amputation through the talonavicular and calcaneocuboid joints, leaving only the hindfoot); Syme ankle disarticulation; transtibial (below knee); knee disarticulation (through knee); and transfemoral (above knee).[6,7] The excision must be proximal to the level of damaged tissue. Other considerations in determining the level of amputation include degree of tissue oxygen perfusion, predicted patient adherence with after-care and lack of protective sensation.[7]

It has been suggested that amputation should not be viewed as failure of management, but rather as a means of restoring a patient's functional status. However, this may depend upon the level of amputation performed. Partial foot excision is considered to have several advantages, including preservation of weight-bearing and proprioceptive abilities, less alteration of body image and modest postoperative requirements for footwear modification or application of a small prosthesis or orthosis. Such devices may help restore near-normal ambulatory function.[7] The term 'proprioceptive' refers to the capability of receiving stimuli originating in muscles, tendons and other internal tissues.[8] However, the short- and long-term success of amputation can depend upon the underlying morbidity at the time of surgery and also future morbidity. A non-systematic review of mainly surgical case series suggested postoperative re-ulceration rates of around 25%.[9] In addition, it has been noted that a proportion of patients undergo repeated amputations of either a higher level of the same limb or the contralateral limb.[5,10,11]

Quality of life

Studies have shown that diabetic people with foot ulceration suffer from reduced quality of life in terms of pain, restricted mobility, time lost from work and reduction in social activities, leading to social isolation and loneliness.[12–14]

A number of studies have attempted to assess the impact of amputation on quality of life in diabetic patients. Three studies reported the surprising finding that some amputees experienced a better quality of life than those with a DFU, at least in some domains.[15–17] In studies where information was given about the level of amputation, the increased quality of life scores in amputees relative to people with a foot ulcer were seen only in those with minor amputations (toe or transmetatarsal).[15,17] This finding may be explained by the possibility that those with a DFU develop depression associated with the acknowledgement of a poorer state of health.[18] In addition, reduced mobility has been shown to be associated with reduced quality of life in diabetic

patients.[13] Those with a DFU often have a regimen of reduced mobility imposed upon them, owing to the requirement to reduce pressure on the affected foot, whereas amputees who have had a prosthesis fitted are normally encouraged to mobilise.[18]

General management of DFU

The management of the patient with a DFU requires input from a multidisciplinary team who provide different aspects of care, as follows:

- patient education
- optimisation of blood glucose control
- correction (where possible) of arterial insufficiency
- reduction of pressure on the foot, for example, through the use of pressure-relieving/redistributing orthoses such as total contact casts
- optimal skin care
- optimal care of wounds, with respect to cleansing and dressings
- debridement of non-viable tissue
- reduction of pain associated with ulceration (particularly arteriopathic ulcers)
- surgical intervention, including debridement, drainage of pus, revascularisation or amputation, as considered necessary
- maintenance of mobility and independence
- prevention of wound infection, where possible
- early detection and treatment of wound infection.

Care may take place in various settings, including primary care, specialist outpatient clinics, hospital (acute care) and rehabilitation centres. Current recommendations state that diabetic patients should be screened regularly and entered on to a register. Those deemed to be at risk of foot problems should be referred to a diabetes foot care team consisting of a physician, a nurse specialist and a podiatrist.[19,20] However, many hospitals in the UK have yet to implement such a team.[21] A recent survey of consultant diabetologists (79/160 usable questionnaires returned) indicated that 67% of respondents had access to a designated diabetic foot clinic. However, the staff members of the clinics were not described.[22]

Wound infection and healing

The presence of a combination of pathophysiological factors means that people with diabetes are particularly susceptible to foot infection. These factors include impaired glycaemic control, neuropathy, altered foot anatomy, lower extremity oedema, peripheral vascular disease, immunodeficiency, impaired wound healing, altered flora on unbroken skin and an increased incidence of skin disorders leading to breaks in the skin.[23,24] Foot ulceration may be viewed as one of a number of clinical signs that can alert the clinician to the development of diabetic foot infection, a broader clinical problem than ulceration alone. Other indicative lesions include cellulitis, abscess, osteomyelitis and an inflamed appearance of the soft tissue of the foot. Other local signs of diabetic foot infection include pain, swelling, sinus tract formation, crepitation (thought to suggest presence of soft tissue gas and necrosis) and fluctuance (thought to indicate undrained suppuration). Systemic signs and symptoms of infection (fever, rigors, vomiting, tachycardia, confusion, malaise) and metabolic disturbances such as severe hyperglycaemia may also indicate a locally developing infection of the foot.[24,25] Although we recognise that diabetic foot infection may occur in conjunction with ulceration, this project will focus on the management of foot ulceration with regard to infection. Therefore, infections of the foot where there is no ulcer present will not be considered for the purposes of this project.

Moist chronic skin ulcers are an ideal medium for microbiological growth and the identified flora can include both aerobic and anaerobic bacteria, and fungi.[24] Results from studies of microbiological cultures from DFUs have indicated that the most frequently identified isolates are as follows:

- Aerobes – *Staphylococcus aureus*, *Staphylococcus epidermidis*, coagulase-negative *Staphylococcus* species, group B *Streptococcus*, *Enterococcus* spp., *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis* and other *Proteus* species[26–36]
- Anaerobes – *Bacteroides melaninogenicus*, *Bacteroides fragilis*, *Peptostreptococcus* species and *Peptococcus* species[27–29,32,33,35–37]
- Fungi – *Candida tropicalis* and *Candida albicans*.[27]

Anaerobes are sometimes mentioned as important causative organisms in DFU infection. Microbiological surveys in DFUs show a wide range of anaerobe prevalence, expressed as a proportion of the total number of isolates found (5–58%).[26–36] This variation may depend upon the setting of the study, the methods used for collecting, transporting and analysing specimens and patient or wound characteristics. It may also

reflect the possible difficulties of culturing anaerobes from routine swabs and/or failure to use prolonged anaerobic culture methods.[38]

Some authors suggest that infection in DFUs may be caused by the presence of more than one isolate.[30,39] In a Canadian study, the mean number of organism types per lesion varied according to the setting of treatment: 2.1 isolates for a university hospital, 2.3 for a community hospital and 3.4 for a district hospital.[30] In a smaller study based in the UK and Ireland, the mean number of isolates cultured from patients attending a diabetic clinic was 4.5 per wound.[39]

It is possible that different microorganisms that are present in the same wound may interact with one another, for example aerobes and anaerobes. An emerging area of research interest is the possible impact of biofilms on outcomes in chronic wounds. A biofilm has been defined as "a layered culture of microorganisms growing on a surface that they have created themselves by secreting polysaccharides and glycoproteins".[8] The structured communities of bacteria within a biofilm are thought to have increased resistance to antimicrobial agents compared with bacteria living as planktonic forms (meaning free-living bacteria as opposed to those contained within biofilm communities).[40,41] Biofilms have been cultured in animal models.[41] In a case series of 15 patients who had undergone vascular grafts, 13 had biofilms cultured from their graft sites during follow-up times ranging from 5 months to 14 years.[42] It has been proposed that the presence of biofilms may have an adverse impact on diabetic foot infections and that therapies other than antimicrobial agents may need to be considered such as enzymatic therapy or inhibition of bacterial communication.[40] However, further research is required in this area to establish the impact of biofilms on outcomes in DFUs and to determine the optimum methods of management.

The eradication of causative microorganisms has been deemed to be an important outcome in the management of infection in DFUs, as reflected in the literature and through expert opinion.[43–47] However, wound healing has also been identified as an important outcome, and may be of greater importance to patients than outcomes such as the resolution of infection.[13,48,49]

The relationship between bacterial colonisation and healing in chronic wounds is currently unclear.[50–53] Although it has been proposed that higher bacterial counts may be associated with failure to heal,[51,54,55,] some sources suggest that the presence of bacteria is unimportant.[50,52] However, other findings indicate that the presence of four or more bacterial groups may be associated with delayed healing.[56] Results from some studies suggest that the presence of specific microorganisms may be detrimental to wound healing, including β-haemolytic streptococci and *Staphylococcus aureus*.[51] However, most of this literature relates to venous leg ulcers. An earlier systematic review did not find any such data on DFUs.[48]

Management of infection in DFU

General treatment considerations

The resolution of infection in DFUs requires a broad consideration of several aspects of clinical management, including optimisation of glycaemic control, surgery (debridement, drainage and revascularisation) and the treatment of associated and concurrent deep soft tissue infection and/or osteomyelitis.

Prolonged, poorly controlled hyperglycaemia is associated with progressive adverse changes in various types of body tissue and abnormalities of the immune system. Impaired glycaemic control is thought to contribute to increased rates of infection, and to generate more serious infections. It is therefore generally recommended that attention be given to optimising blood glucose levels in any diabetic patient with an infected foot or ulcer.[57]

Surgical procedures may also have a role in managing infected DFUs. Sharp or surgical debridement may help counter wound infection through the removal of necrotic tissue, which can foster microorganisms.[24,25,58] Surgical drainage of pus can be deemed necessary if the infected ulcer is associated with a deeper soft tissue infection.[24] The presence of vascular disease impairs the delivery of antibiotics and oxygen to areas of infection.[58] Vascular reconstruction surgery to treat peripheral arterial disease may help resolve infection by improving the blood flow to the foot, thereby improving the supply of nutrients and drugs to infected tissue.[24,25,58]

Long-term and refractory infection of DFUs may be associated with the presence of underlying osteomyelitis.[58] Findings from a small, non-randomised study suggested that conservative surgical treatment of osteomyelitis added to medical treatment may produce an increased healing rate of foot ulcers compared with medical

treatment alone.[59] The potential importance of the above therapies in treating infected DFUs is acknowledged. However, this project will focus on the diagnosis of infection and use of antimicrobial agents in the management of DFUs.

Diagnosis of infection in DFUs

Diagnostic aspects of infection in DFUs focus on the identification of infection through clinical judgement and/or laboratory techniques. The acquisition of microbiological specimens is required in order to culture potentially causative microorganisms and study their sensitivities to antibiotic therapy; however, when more than one bacterial species is identified it is difficult to determine which is/are causing the infection. Acquisition techniques include the wound swab, curettage, tissue biopsy and fine-needle aspiration.[24,60] Two more recently developed, potentially useful techniques are the electronic nose/tongue and polymerase chain reaction (PCR). The electronic nose/tongue is a type of electronic sensor used to detect the presence of bacteria. It has been used in rhinological research[61] and for *in vitro* studies.[62] PCR is a system for the *in vitro* amplification of DNA, amplification in this context being an increase in the number of copies of a specific DNA fragment.[8] This technique has been used for detecting resistant staphylococcal infection following cardiac surgery[63] and in burns patients.[64] It may be useful in cases where suspected bacterial presence cannot easily be detected using culture techniques,[65] where the cultivation of a causative microorganism is considered to be risky[66] or where a pathogen is known to be slow-growing.[67] Relevant evidence relating to these newer techniques, and also the more established bacterial acquisition methods, will be sought and assessed in this review. Of the currently available techniques, it could be argued that wound swabs are the most important as they are performed more frequently than the other methods. There is an important related debate about whether techniques and procedures used for swabbing and plating out (spreading a specimen onto a nutrient surface) are always optimal.[56]

The interactions between clinical assessment, microbiological sampling and antibiotic prescribing are of importance in the management of DFU. There is some debate in the literature as to whether it would be advisable to wait for bacteriology results prior to prescribing antibiotics in order to ensure that the correct agent is administered, or whether to give antibiotics before the result has been reported. Early treatment without the test result might be beneficial as it may promote faster healing and help to reduce amputation rates. However, it could also mean that the wrong antibiotics are prescribed, which may encourage bacterial resistance. Another approach is not to rely on cultures at all, but to treat the wound according to clinical judgement.[24,25]

Several different study designs may be considered for primary evaluations of diagnostic tests. It is possible to combine diagnostic and treatment components of clinical management in a diagnostic randomised controlled trial (RCT). Such studies combine an evaluation of the performance of diagnostic tests and subsequent treatment strategies in a sequential design, capturing the eventual effect of diagnostic procedures on clinical outcomes. Just as in evaluations of the clinical effectiveness of a therapy, this design is considered optimal.[68,69] Diagnostic RCTs have been conducted in areas such as acute appendicitis[70–71] and developmental hip dysplasia.[72]

Alternative designs in diagnostic research include case–control and cohort studies. When compared with a diagnostic RCT, these study designs are more prone to bias. Important types of bias in diagnostic research include the following:[68,69]

- Spectrum bias (occurs when the group recruited to the study is not representative of the population to which the test will be applied in clinical practice).
- Absent, inappropriate or imperfect reference standard.
- Rapid developments in technology, meaning that study findings rapidly become obsolete.
- Disease progression bias (patients may get better or worse over time owing to the time lag between the application of the index and reference tests).
- Partial verification bias (only some patients receive the reference test).
- Differential verification bias (inconsistent reference standards used).
- Incorporation bias (index test is part of the reference standard).
- Treatment paradox (improvement of condition due to treatment given, usually following the results of the index test).
- Review bias (failure to blind to findings of index and/or reference test).
- Clinical review bias (interpretation influenced by availability of clinical data).
- Inappropriate handling of unclear results in the data analysis (i.e. failure to report them clearly).
- Arbitrary choice of threshold value (especially if determined *post hoc*).

Diagnostic cohort and case–control studies are seen more frequently in the literature than diagnostic RCTs, and therefore evidence from these designs is likely to be of value, provided that the potential impact of important sources of bias can be taken into account.[68,69]

Systemic antimicrobial agents

Systemic treatments for infection in DFUs revolve around the prescription of antibiotics. Systemic agents can be administered orally for mild to moderate infections or intravenously for more serious infections, and usually fall into the following groups:[73]

1. penicillins, for example flucloxacillin and amoxicillin
2. cephalosporins, cephamycins and other β-lactams, for example cefalexin and cefazolin
3. tetracyclines (oral route only), for example tetracycline
4. aminoglycosides (given by the intramuscular or intravenous route), for example gentamicin and netilmycin
5. macrolides, for example erythromycin and clarithromycin
6. quinolones, for example ciprofloxacin.

There are also several other drugs available, including clindamycin, metronidazole and trimethoprim.[73] A previously published systematic review including only studies reporting objectively assessed wound healing outcomes found two small RCTs of oral antibiotics used with DFUs. In terms of wound healing, oral amoxycillin combined with clavulanic acid proved to be no better than placebo,[74] and no statistically significant difference was observed between clindamycin and cephalexin.[75] Despite this paucity of existing evidence, current recommendations for DFU care include systemic antibiotics as considered necessary in conjunction with cleansing, debridement, wound dressings, pressure relief and good glycaemic control.[23,49,76–79]

Topical antimicrobial agents

Topical preparations may be divided into two categories, according to their function. One group consists of lotions with antimicrobial properties, used to irrigate or cleanse wounds. These usually have only a brief contact time with the wound surface, unless they are used as a pack or soak. They include the hypochlorites (e.g. Eusol), hexachlorophene (hexachlorophane) – a constituent of some soaps and other skin cleansers – and substances such as potassium permanganate and gentian violet (both used in solution).[73]

The second group consists of preparations designed to stay in contact with the wound surface for a longer period of time, ideally until the next dressing change. These include creams, ointments and impregnated dressings. Most topical antibiotics come into this category, and include mupirocin, fusidic acid and neomycin sulfate. Other preparations include silver-based products, such as silver-sulfadiazine.[73]

Products that fall into both categories include povidone-iodine, chlorhexidine and hydrogen peroxide.[73]

An emerging topical agent is pexiganan acetate, a peptide antibiotic.[24]

Methods used in this project

Systematic reviews may be based on evaluations of diagnostic tests and evaluations of clinical effectiveness. On occasions, a series of such reviews may be required to answer a complex research question, as opposed to the single reviews that are often seen in the literature. Systematic reviews are most commonly used to address individual and focused research questions about the effects of healthcare interventions.[80] However, health professionals usually view patients in the context of a more complex sequence of decisions and associated interventions. Decision analysis is a technique that allows representation of this more complicated scenario.[81]

Clinical decision analysis is a modelling technique that represents the different pathways of care that are possible for a given patient together with the complex sequence of decisions involved in that care. It is a useful technique for helping health professionals to identify the optimum pathway of care under conditions of uncertainty.[82] Some of the advantages of clinical decision analytic models include the option of being able to undertake sensitivity analyses if there is uncertainty around important model parameters, patient preferences can be incorporated into the model and decisions, preferences and utilities can be made explicit.[82]

Initial representation of pathway of care

In order to make the linkages between the diagnostic and effectiveness questions explicit, we will describe a theoretical pathway of care, highlighting the decisions made by clinicians at

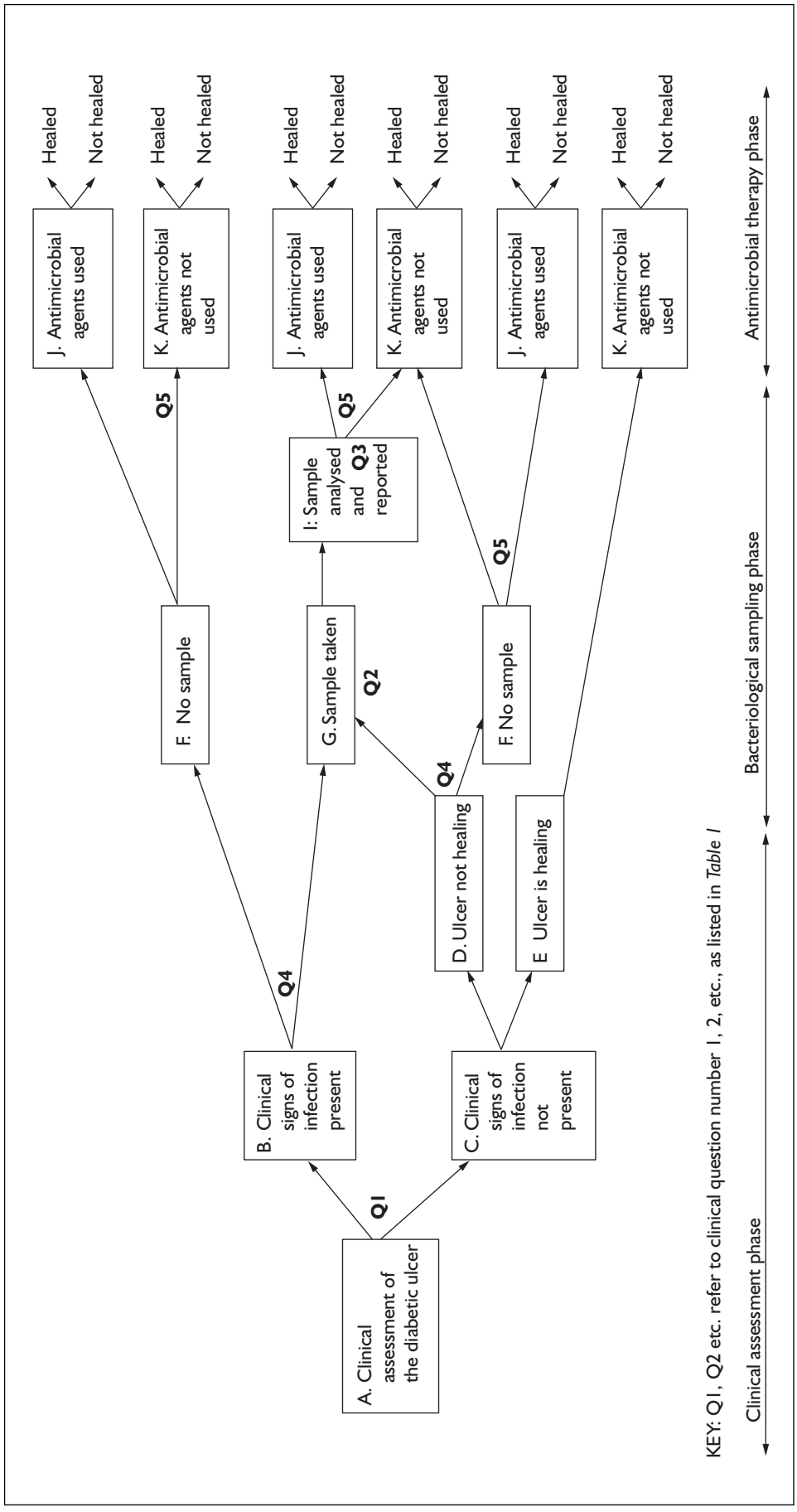


FIGURE 1 *Initial clinical pathway for treatment of potentially infected DFUs*

various stages. *Figure 1* is a simple representation of the decisions made in the treatment of a potentially infected DFU. This pathway was constructed at the start of the project to help represent the interdependence of the various decisions that can be made. It was amended during the project from the literature and the final pathway is shown in *Figure 8* (p. 59). This pathway integrates the methods of diagnosis of infection, the decision to treat immediately or await results of an antibiogram and the effectiveness and cost-effectiveness of individual antimicrobial agents (an antibiogram has been defined as an examination that measures the biological resistance of substances causing disease, performed prior to chemotherapy so as to make it more efficient).[83] This simplified pathway does not take into account the transitions of an ulcer from uninfected to infected status or the pathway of care for those ulcers that are unhealed at the end of this episode. It does serve, however, to illustrate the combination of clinical questions and decisions that inform the care of a person with a diabetic foot ulcer. At the very left of the pathway, at the point where a patient enters the system, a clinical assessment is undertaken to assess for the presence of infection. The clinical pathway followed depends on the result of this assessment.

A person with an ulcer that appeared infected would follow the route A–B. At this point, the clinician decides whether to take a microbiological sample to inform therapy or to treat empirically. A clinician makes this decision when they reach box B, that is, do the advantages of waiting for bacteriology results outweigh the benefits of immediate, empirical treatment? The route F–J represents empirical treatment, whereas the route G–I–J represents taking a sample to inform choice of antimicrobial agent.

If the decision is made to take a sample to inform microbiological therapy, then the clinician makes a choice from a number of types of sampling techniques, such as biopsy, swab or near-patient testing techniques for bacteria such as the electronic nose. The clinician makes the decision about choice of sample at box G. We need to know whether, for example, a wound swab is a valid indicator of the presence of infection. Following the collection of a bacteriological sample, a subsequent decision may need to be made regarding the sample processing, for example, qualitative culture and sensitivity, quantitative or semi-quantitative culture or techniques using DNA replication to expand and identify bacterial populations. The decision about the processing and analysis of the sample is made at box I.

A person with an ulcer that appeared uninfected and yet failed to heal may also be offered antimicrobial therapy as the clinician may suspect that the wound is in fact infected without displaying signs and symptoms of infection. The pathway A–C–D would represent this situation. At point D in the pathway, the clinician decides whether to treat empirically or to take a microbiological sample to inform therapy.

A patient whose ulcer is not clinically infected and whose ulcer is healing satisfactorily will not usually be offered antimicrobial agents and would follow the pathway A–C–E–K.

At each decision point, there is the potential for the results of the systematic reviews of the performance of diagnostic tests or the clinical and cost-effectiveness of antimicrobial therapy to guide clinical decisions/sampling policies. Patient preferences may also be taken into account. The points at which the review questions (1–5, see *Table 1*) are addressed are also highlighted in *Figure 1*.

Chapter 2

Research questions

The aim of this research is to define the optimum management strategies for infected DFUs with reference to clinical examination, microbiological sampling of the wound and antimicrobial therapy.

This research had two objectives:

1. to undertake a series of systematic reviews of the evidence relating to the diagnosis and treatment of infection in DFU
2. to use estimates derived from the systematic reviews to create a decision analytic model

Five linked systematic reviews were conducted, three concerning aspects of diagnosis, one focusing on effectiveness of microbiological analysis and the other on both clinical and cost-effectiveness of antimicrobial treatment. The research questions and corresponding systematic reviews are outlined in *Table 1*.

TABLE 1 *Research questions and corresponding systematic reviews*

Question	Systematic review of
1. How can clinicians determine whether a sample should be taken from a DFU?	… the sensitivity and specificity of clinical examination in the identification of infection in DFUs
2. What sampling techniques are the most accurate for people with DFUs?	… the sensitivity and specificity of different sampling techniques (wound swab, biopsy, wound lavage and/or curettage, near-patient testing techniques) in the identification of infection in DFUs
3. What laboratory techniques are the most accurate for analysing samples from DFUs?	… the sensitivity and specificity of techniques of microbiological analysis (qualitative, quantitative, semi-quantitative) in the identification of infection in DFUs
4. What impact does microbiological analysis have on therapy?	… the effects of microbiological analysis on the treatment of infection, pain (in patients without neuropathy), exudate associated with DFUs, the impact on healing, impact on HRQoL and the development of complications
5. What is the effectiveness and cost-effectiveness of management of infection in DFU?	… the clinical effectiveness and cost-effectiveness of techniques for treating infection in DFUs including wound healing and the transfer of drug-resistant organisms to staff and other patients

Chapter 3

Review methods

Search strategy

Search strategies and bibliographic databases used

We searched 19 electronic databases, two Internet sources of ongoing research, six conference proceedings, one journal and three books for primary research or systematic reviews, and nine Internet sources for clinical practice guidelines or reviews. All sources were searched for diagnostic, effectiveness and modelling studies. For the diagnostic questions we searched for systematic reviews of diagnostic studies, primary diagnostic studies, and economic evaluations of diagnostic studies. For the effectiveness questions, we searched for systematic reviews of trials [RCTs and/or controlled clinical trials (CCTs)], primary studies (RCTs and/or CCTs) or economic evaluations of intervention studies. For the modelling question we searched for decision analytic or economic models. The sources are listed in *Table 2*.

The searches were carried out in three stages. The first set of searches aimed to retrieve papers relating to clinical effectiveness, the second papers relating to economic effectiveness and the third to diagnostic testing. All three sets of retrieved records were then imported into reference manager software (Endnote) and labelled as either 'rct', 'econ' or 'diag' depending on the search strategy from which they were retrieved. These records were then de-duplicated and any records that were retrieved from more than one of the search types labelled as such.

Diagnostic searches

Literature searches were carried out on sampling and microbiological techniques for the diagnosis of DFUs. Databases were searched from the date of inception of each database to the most recent date available.

Internet databases

- Allied And Complementary Medicine (AMED) (1985–2002 November).
  Searched: 23 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- British Nursing Index (BNI) (1994–2002 September).
  Searched: 23 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- CINAHL (1982–2002 October, week 4).
  Searched: 23 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- EMBASE (1980–2002, week 46).
  Searched: 24 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- MEDLINE (1966 to 2002 October, week 5).
  Searched: 24 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- PREMEDLINE (up to 21 November 2002).
  Searched: 24 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.

Handsearches

Six conference proceedings, the *Diabetic Foot* journal and three books were handsearched.

Clinical effectiveness searches

The following sources were searched for studies relating to the impact of microbiological analysis on therapy and the effectiveness of different treatments. The literature searches were designed to retrieve systematic reviews and trials only. However, some databases cannot be reliably restricted by study type and in these cases the search was not limited by study design, and the results of the searches were entered into an Endnote Library. A range of free text terms and subject headings were used as appropriate. Details of the search strategies are contained in Appendix 1.

CRD internal administration databases (searched: 12 November 2002 using CAIRS software)

- Database of Abstracts of Reviews of Effectiveness (DARE).
- Health Technology Assessment Database (HTA).

Internet databases

- Allied And Complementary Medicine (AMED) (1985–2002 November).
  Searched: 12 November 2002 OvidWeb Gateway at http://gateway.ovid.com/athens.
- British Nursing Index (BNI) (1994–2002 August).
  Searched: 6 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- CINAHL (1982–2002 October, week 4).
  Searched: 6 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.

TABLE 2 *Sources for primary studies, reviews and guidelines*

Electronic databases
- Allied and Complementary Medicine Database (AMED)
- British Nursing Index (BNI)
- Cochrane Controlled Trials Register (CCTR)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Specialised Wounds Register
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Database of Abstracts of Reviews of Effects (DARE)
- DH-Data
- EconLit
- EMBASE
- Health Economic Evaluation Database (HEED)
- Health Management Information Service Database (HELMIS)
- Health Technology Assessment (HTA) database
- Index to Scientific and Technical Proceedings (ISTP)
- King's Fund Database
- MEDLINE
- MEDLINE In Process
- NHS Economic Evaluation Database (NHS EED)
- System for Information on Grey Literature in Europe (SIGLE)

Additional sources to identify ongoing research
- Controlled Clinical Trials (http://controlled-trials.com)
- National Research Register (NRR) (http://www.nrr.nhs.uk/search.htm)

Handsearching conference proceedings
- 3rd International Conference on the Diabetic Foot, Noordwijkerhout, The Netherlands, 1999
- Diabetic Foot Study Group meeting: Fiuggi, Italy, 2000; Crieff, Scotland, 2001; Balaton, Hungary, 2002
- 8th and 9th Malvern Diabetic Foot Conferences, 2000 and 2002

Handsearching journals and books
- Journal: *The Diabetic Foot*
- Books: *The Foot in Diabetes*. Boulton AJM, Connor H and Cavanagh PR, editors. 3rd edition, Wiley, Chichester, 2000
- *Levin and O'Neal's The Diabetic Foot*. Bowker JH and Pfeifer MA, editors. 6th edition, Mosby, St Louis, MO, 2001
- *The Evidence Base for Diabetes Care*. Williams R, Herman W, Kinmonth AL and Wareham NJ, editors. 2002

Internet searches to identify review/guideline documents
- Clinical Evidence (http://www.clinicalevidence.com/)
- Health Evidence Bulletins Wales (http://www.uwcm.ac.uk/uwcm/lb/pep)
- Health Services Technology Assessment Text (HSTAT) (http://text.nlm.nih.gov/)
- National Coordinating Centre for HTA (http://www.hta.nhsweb.nhs.uk)
- National Guideline Clearing House (http://www.ahcpr.gov/clinic/assess.htm)
- National Institute for Health and Clinical Excellence (NICE) web page (published appraisals) (http://www.nice.org.uk/nice-web/)
- ScHARR Lock's Guide to the Evidence (http://www.shef.ac.uk/uni/academic/R-Z/scharr/ir/scebm.html)
- Scottish Intercollegiate Guidelines Network (SIGN) (http://www.sign.ac.uk)
- Turning Research Into Practice (TRIP) (http://tripdatabase.com)

- Cochrane Controlled Trials Register (CCTR) (2002: Issue 4).
  Searched: 12 November 2002 on Internet Explorer using the "new generation software" at http://www.update-software.com/cochrane/.
- Cochrane Database of Systematic Reviews (CDSR) (2002: Issue 3).
  Searched: 12 November 2002 on Internet Explorer using the 'new generation software' at http://www.update-software.com/cochrane/.
- EMBASE (1980–2002, week 44).
  Searched: 6 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- MEDLINE (1966–2002 October, week 4).
  Searched: 6 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- PREMEDLINE (up to 5 November 2002).
  Searched: 6 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.

Handsearches

Six conference proceedings, the *Diabetic Foot* journal and three books were handsearched.

No date or language restrictions were applied to any of the literature searches. The bibliographies

of all included studies were examined in order to identify any additional relevant studies.

Cost-effectiveness and modelling searches

Those databases restricted by study design in the clinical effectiveness searches were searched again with a search strategy designed to retrieve cost-effectiveness studies, decision models or economic models. Two specialist databases were also searched, the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluation Database (HEED); no economic filter was necessary for these databases.

CRD internal administration databases

- NHS EED (searched 13 November 2002 on CAIRS software).

CD-ROM resources

- EconLit (1969–2002 October)
  Searched: 12 November 2002 on ARC SilverPlatter
- HEED (Issue: November 2002)
  Searched: 13 November 2002 on stand-alone CD-ROM

Internet databases

- Allied and Complementary Medicine Database (AMED) (1985–2002 November).
  Searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- British Nursing Index (BNI) (1994–2002 August).
  Searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- CINAHL (1982–2002 October week 4).
  Searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- EMBASE (1980–2002 week 44).
  Searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- MEDLINE (1966–2002 October, week 5).
  Searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.
- PREMEDLINE (up to 11 November 2002).
  Searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens.

Handsearches

Six conference proceedings, the *Diabetic Foot* journal and three books were handsearched.

Generic searches

There were a number of databases for which it was not practical to justify searching separately for clinical, cost-effectiveness and diagnosis studies because the database was either too small to warrant such a detailed search or the interfaces for the database were too simplistic. A general search for papers on DFUs was therefore sufficient for the following databases and the papers were then sifted for relevance.

Internet resources and databases (searched: 26 August 2002)

- Health Evidence Bulletins Wales
  http://www.uwcm.ac.uk/uwcm/1b/pep
- Health Services Technology Assessment Text (HSTAT)
  http://text.nlm.nih.gov/
- Index to Scientific and Technical Proceedings (ISTP) (1990 onwards)
  http://wos.mimas.ac.uk/
- National Coordinating Centre for Health Technology Assessment
  http://www.hta.nhsweb.nhs.uk
- National Guideline Clearinghouse
  http://www.ahcpr.gov/clinic/assess.htm
- National Institute for Health and Clinical Excellence (NICE) (published appraisals)
  http://www.nice.org.uk/nice-web/
- Scottish Intercollegiate Guidelines Network (SIGN) Guidelines
  http://www.sign.ac.uk/
- Turning Research Into Practice (TRIP) Index
  http://www.ceres.uwcm.ac.uk/framset.cfm?section=trip

CD-ROM resources

- Health Management Information Consortium (HMIC) Databases: HELMIS 1984–1998/DH-Data and King's Fund Database 1983–2002/King's Fund Database 1979–2002.
  Searched: 09 November 2002 on ARC SilverPlatter).
- National Research Register (NRR) (2002, Issue 4).
  Searched: 13 November 2002 on stand-alone CD-ROM.
- SIGLE (1967–2002 July, week 3).
  Searched: 06 November 2002 on ARC SilverPlatter.

Study selection

References identified from the search strategies were de-duplicated and entered into a bibliographic software package (ProCite Version 5 for Windows). Titles and abstracts, where available, were examined by two reviewers. If either reviewer considered a reference to be potentially relevant, the full report was retrieved. Full reports were screened for inclusion with close reference to the

inclusion criteria described below. At both stages of study selection, two reviewers made decisions independently and met subsequently to discuss disagreements. Any disagreements were resolved by discussion. No restrictions were applied in terms of the date of publication or the language of the report.

Inclusion criteria for systematic reviews of diagnosis (questions 1–3)

1. The study must compare the results of an independent gold standard (as defined in the study) with an alternative assessment.
2. The target population must comprise patients with diabetes mellitus aged 18 years or older with a foot ulcer. Since it was expected that the body of literature relating to diagnosis of infection in DFUs would be small, trials recruiting adults with venous leg ulcers were also eligible for inclusion for questions 1–3. It was considered that although the focus of this project should remain the management of patients with infected DFUs, it is possible that useful information may be obtained from the venous leg ulcer literature as techniques for obtaining and analysing samples are likely to be similar, regardless of wound aetiology.
3. Sufficient data must be presented in the paper to enable completion of a 2×2 diagnostic table (true positives, false positives, true negatives, false negatives), thus allowing outcomes such as sensitivity, specificity, predictive values and likelihood ratios to be calculated.

Inclusion criteria for systematic review of impact of microbiological analysis on therapy or outcomes (question 4)

1. The study must be an RCT or a CCT of one or more strategies of managing suspected infection of DFUs, such as empirical therapy versus microbiological analysis and the use of appropriate antimicrobial regimens. A CCT was defined as a prospective non-randomised comparative study with concurrent study groups.
2. The target population must comprise patients with diabetes mellitus aged 18 years or older with a foot ulcer. Studies recruiting solely people with diabetic foot infection or osteomyelitis without ulceration were not included.
3. The study must compare policies of prescribing antimicrobial agents (i.e. wait for result of microbiological analysis before administration versus administration without test result). Evaluations of relevant strategies/policies delivered in any healthcare setting were considered for inclusion in the review.
4. At least one of the following outcome measures must be reported:
   (a) mortality (all or related to amputation)
   (b) incidence and type of amputation
   (c) incidence of osteomyelitis
   (d) pain (in patients without neuropathy)
   (e) proportion of ulcers healing
   (f) time to complete healing
   (g) change in ulcer area (absolute or relative)
   (h) healing rate
   (i) change in ulcer depth or volume (absolute or relative)
   (j) ulcer recurrence
   (k) number and duration of hospital admissions for diabetic foot problems
   (l) bacterial profile of ulcer
   (m) acquisition of resistant organisms
   (n) relationship between ulcer healing and bacteriology
   (o) change in mobility
   (p) change in level of dependence/independence
   (q) impact on health-related quality of life.

The most important outcomes were considered to be those relating to mortality, amputation and wound healing. However, evaluations reporting any of the outcomes described above were considered for inclusion. In addition, data on adverse events and adherence were recorded, where available. Large cohort/population studies would be needed to identify rare adverse events, such as the acquisition of resistance, and we did not search for these as there are poorly developed methods of searching for these study designs and there was insufficient time within this project to undertake this.

Inclusion criteria for systematic review of clinical effectiveness (question 5: part 1)

1. The study must be an RCT or a CCT of one or more antimicrobial regimens (the comparator can include no intervention, placebo or standard care). A CCT was defined as a prospective non-randomised comparative study with concurrent study groups.
2. The target population must comprise patients with diabetes mellitus aged 18 years or older with a foot ulcer. Studies recruiting solely people with diabetic foot infection or osteomyelitis without ulceration were excluded.
3. The study must evaluate an antimicrobial agent used with the primary intention of treating infection in DFUs. Evaluations of relevant interventions delivered in any healthcare

setting were considered for inclusion in the review. Evaluations of interventions possibly influencing healing that might be used concurrently with antimicrobial agents (e.g. pressure relief, optimisation of blood glucose control, improvement of blood supply to the foot) were excluded.

During the process of screening studies for eligibility, it was noted that several trials included mixed populations, for example, people with soft tissue infection who did not all necessarily have foot ulceration or diabetes. Separate outcomes for the patients with DFU were not always reported in the papers and, in some cases, authors were not able to supply the stratified data. Recognising that useful evidence could still be gleaned from a mixed population study where the majority of patients had a DFU, a *post hoc* decision was taken to include such studies in the review on condition that it could be ascertained that at least 80% of recruited patients had a DFU.

4. At least one of the following outcome measures must be reported:
   (a) mortality (all or related to amputation)
   (b) incidence and type of amputation
   (c) incidence of osteomyelitis
   (d) pain (in patients without neuropathy)
   (e) proportion of ulcers healing
   (f) time to complete healing
   (g) change in ulcer area (absolute or relative)
   (h) healing rate
   (i) change in ulcer depth or volume (absolute or relative)
   (j) ulcer recurrence
   (k) number and duration of hospital admissions for diabetic foot problems
   (l) bacterial profile of ulcer
   (m) acquisition of resistant organisms
   (n) relationship between ulcer healing and bacteriology
   (o) change in mobility
   (p) change in level of dependence/independence
   (q) impact on health-related quality of life.

The most important outcomes were considered to be those relating to mortality, amputation and wound healing. However, evaluations reporting any of the outcomes described above were considered for inclusion. In addition, data on adverse events and adherence with the treatment regimen were recorded, where available.

Inclusion criteria for systematic review of economic evaluations (question 5: part 2)

Economic evaluations were considered for inclusion if they focused on the diagnosis and/or treatment of infected DFUs and if they reported a synthesis of associated costs and benefits. Evaluations of any diagnostic test or antimicrobial treatment strategy in infected diabetic foot ulcers were eligible. Any type of economic evaluation was eligible, including cost-effectiveness analysis, cost–benefit analysis, cost–utility analysis or cost-minimisation analysis.

Data extraction

Details of eligible studies were extracted and summarised using a structured data extraction table (see Appendix 3). If data were missing from reports, then attempts were made to contact the authors to obtain sufficient data to carry out data extraction and critical appraisal. Multiple publications of the same study were regarded as a single report and all relevant details were recorded. Two reviewers verified data extraction independently. Disagreements were resolved by discussion.

Critical appraisal of included studies

Three separate checklists were used for diagnostic studies, effectiveness studies and economic evaluations. Two reviewers performed critical appraisal of each individual included study independently. Disagreements in judgements about methodological quality were resolved through discussion.

Critical appraisal of diagnostic studies

A 12-item checklist known as QUADAS (Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews)[84] was used (*Table 3*). This was generated using evidence-based methods combined with a Delphi procedure. The checklist was accompanied by a guide for completion that aims to minimise subjective judgement.[84] Where an item is scored as 'unclear', this refers to the quality of reporting within the paper rather than the methodological quality of the diagnostic evaluation.

Critical appraisal of effectiveness studies

The methodological quality of all included RCTs was assessed using a validated five-point scale,[85]

TABLE 3 *Critical appraisal of diagnostic studies checklist – the QUADAS[84] tool*

Item		Yes	No	Unclear
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?			
2.	Were selection criteria clearly described?			
3.	Is the reference standard likely to correctly classify the target condition?			
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?			
5.	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?			
6.	Did patients receive the same reference standard regardless of the index test result?			
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?			
8a.	Was the execution of the index test described in sufficient detail to permit replication of the test?			
8b.	Was the execution of the reference standard described in sufficient detail to permit its replication?			
9a.	Were the index test results interpreted without knowledge of the results of the reference standard?			
9b.	Were the reference standard results interpreted without knowledge of the results of the index test?			
10.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?			
11.	Were uninterpretable/intermediate test results reported?			
12.	Were withdrawals from the study explained?			

and the allocation concealment criterion described by Schulz,[86] as follows:

1. *Randomisation. Score: 0 or 1 or 2*
   One point was given if the study described using words such as random or randomisation. One extra point was given if the method of randomisation was described and was appropriate. One point was deducted if the method of randomisation was described and was considered to be inappropriate.
2. *Double-blinding. Score: 0 or 1 or 2*
   One point was given if the study was described as double-blind. One extra point was given if the method of double-blinding was described and was appropriate. One point was taken away if the method of double-blinding was described and was inappropriate.
3. *Withdrawals. Score: 0 or 1*
   One point was given if the number and reasons for withdrawals in each group were stated.
4. *Allocation concealment. Score: A or B or C*
   (A) Adequate: if adequate measures were taken to conceal allocation.
   (B) Unclear: if report of allocation concealment was not reported or did not fit in category A or C.
   (C) Inadequate: trials in which allocation concealment was inadequate.

The critical appraisal of CCTs included the points above, with the exception of the first (randomisation). In CCTs, the following additional items were assessed: method of allocation to treatment groups; degree of baseline comparability between treatment groups; and appropriateness of adjustment during data analysis for observed imbalances between treatment groups.

Critical appraisal of economic evaluations

The following checklist was used:[87]

1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given?
3. Was the effectiveness of the programmes or services established?
4. Were all the important and relevant costs and consequences for each alternative identified?
5. Were costs and consequences measured accurately in appropriate physical units?
6. Were costs and consequences valued credibly?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis of costs and consequences of alternatives performed?

9. Was allowance made for uncertainty in the estimates of costs and consequences?
10. Did the presentation and discussion of study results include all issues of concern to users?

Data analysis

Questions 1–3: diagnosis

The included studies were summarised using a narrative description. Meta-analysis was considered where studies were considered to be sufficiently similar with respect to patient characteristics and the index and reference tests used. In this case, standard methods for combining primary studies were to be followed.[88] Statistical analysis of the receiver operating characteristic (ROC) curve was performed using SPSS version 12.0.2 and the plot was generated using Excel 2000.

It was planned to analyse studies recruiting patients with venous leg ulcers separately to those of DFU patients. Findings from venous leg ulcer studies were interpreted with great caution when considering any implications for DFUs. For DFUs, it was planned to group studies according to the type of diabetes (type 1 and type 2) and type of foot ulcer (neuropathic and neuroischaemic).

Question 4: effect of microbiological analysis

The included studies were summarised using a narrative description. Meta-analysis was considered if studies were deemed to be sufficiently similar with respect to patient characteristics, interventions and outcomes.

Question 5(1): clinical effectiveness

The included studies were summarised using a narrative description. Meta-analysis was considered if studies were deemed to be sufficiently similar with respect to patient characteristics, interventions and outcomes.

Methods of meta-analysis for questions 4 and 5(1)

The method of synthesising the studies would depend upon the quality, design and heterogeneity of studies identified. Clinical heterogeneity would be explored by examining factors that may impact on outcomes such as care setting and test, patient and ulcer characteristics. Statistical heterogeneity was assessed using a χ^2 test. In the absence of clinical heterogeneity and in the presence of statistical heterogeneity, a random effects model was used for pooling. The summary statistic used depended on the event rate observed. Where the event rate was over 30%, the relative risk (RR) was employed. When the event rate was less than 30%, a summary odds ratio was calculated. Where there was no clinical or statistical heterogeneity, a fixed effects model was applied.

Question 5(2): cost-effectiveness

Each included economic evaluation was described in a narrative fashion. In addition, the use of a summary grading for each evaluation was considered, according to the direction of cost-effectiveness estimates. A matrix was used (*Box 1*) in order to indicate when a clear decision may be made on the basis of the evidence presented (i.e. better health outcomes with lower costs, or poorer health outcomes with higher costs, cells G and C, respectively). Situations where decisions were less favoured (either costs are lower or health outcomes are better) were represented by cells D, B, F and H. Cases where a financial or clinical trade-off was required are shown in cells A and I. Cell E represents a case where no differences were observed between the competing strategies. The position of each individual evaluation within the matrix has been shown.[87,89] Although this method gives a useful summary of results, and is particularly helpful when the results of several economic evaluations are presented, the findings of each individual economic evaluation should be interpreted in the light of methodological quality (see checklist above).

Decision analytic model

The first step in the construction of the model was to conduct a review of the literature to identify any models that described the natural history of patients with DFUs, and to identify studies that could inform the transitions within a decision analytic model. We searched for economic models or decision analytic models, that is, studies in which a mathematical structure had been used to represent the health and/or economic outcomes of patients with a DFUs. *Table 2* describes the sources used to identify research. The results of all searches were scrutinised to identify potentially relevant studies. We planned to model explore the cost-effectiveness of different strategies for managing people with DFUs. The model combines information on the precision of diagnostic tests with clinical consequences of undertaking those tests, for example, which treatment strategies are chosen (cost, amputation

		Incremental effectiveness		
		+	0	–
Incremental costs	+	A	B	C
	0	D	E	F
	–	G	H	I

Decision strongly favoured
G = Accept treatment
C = Reject treatment

Decision less favoured
D = Accept treatment
B = Reject treatment
F = Reject treatment
H = Accept treatment

No obvious decision
A = Is the added benefit worth the cost?
I = Is the reduced effect acceptable given reduced costs?
E = Neutral cost and effect. Other reasons to adopt treatment?

Key:	Effectiveness	Cost
+	Better	Higher
0	Same	Same
–	Poorer	Lower

BOX 1 *Permutation matrix for possible outcomes of economic evaluations for studies of intervention versus comparator*[87,89]

rates, healing times) to variations in the methods of sampling, analysis and treatment regimens. In this way, the area of greatest uncertainty can be identified and this can be used to identify priority areas of future research. For example, it may be possible to recognise whether the priority should be to investigate the sensitivity and specificity of methods of sampling, or to assess the impact of antibiotic therapy on the likelihood of healing. Hence, the decision analysis combines information on the precision of diagnostic tests with clinical consequences of undertaking those tests, for example, which treatment strategies are chosen.

A full description of the methods for constructing the decision analytic model and the outputs is given in the section 'Decision analytic modelling' (p. 48).

Chapter 4

Results

Literature search results

A total of 4225 studies were identified as being potentially relevant to the reviews in our diagnostic, effectiveness and economics searches, of which 14% were identified in more than one search (see *Figure 2*).

Diagnostic studies are summarised first, then the effectiveness studies and cost-effectiveness studies. Finally, the decision analytic model results are described. Data extraction sheets and summary quality assessment tables are summarised in Appendix 5. Studies thought to be relevant from title and/or abstract but excluded after scrutiny for the diagnostic, effectiveness and economic searches are summarised in the excluded studies tables in Appendix 6.

Studies included in the diagnostic review

In the diagnostic review search we identified 2762 study citations, of which 219 were retrieved (three included and 216 excluded). The reasons for exclusion were as follows:

Reasons for exclusion	*N*
Population not DFU	1
2 × 2 data not available	9
Study of inter-observer variation	2
No verification of infection	6
Description of signs/symptoms	1
Description of diagnostic techniques	1
Osteomyelitis diagnosis	43
Diabetic foot infection (not ulcer infection)	8
Systematic review of osteomyelitis	2
Prevalence studies/other reasons	163

Results of diagnostic review

Three eligible diagnostic studies were identified.[90–92] All three recruited patients with a variety of chronic wounds (including DFUs), and were conducted in the USA. One study evaluated the diagnostic performance of clinical examination using tissue biopsy as the reference standard (relates to review question 1),[90] one study assessed wound swab against tissue biopsy as a method of specimen acquisition (relates to review question 2)[91] and the third focused on methods of laboratory analysis of the wound swab, namely semi-quantitative analysis versus quantitative analysis as the reference standard (relates to review question 3).[92]

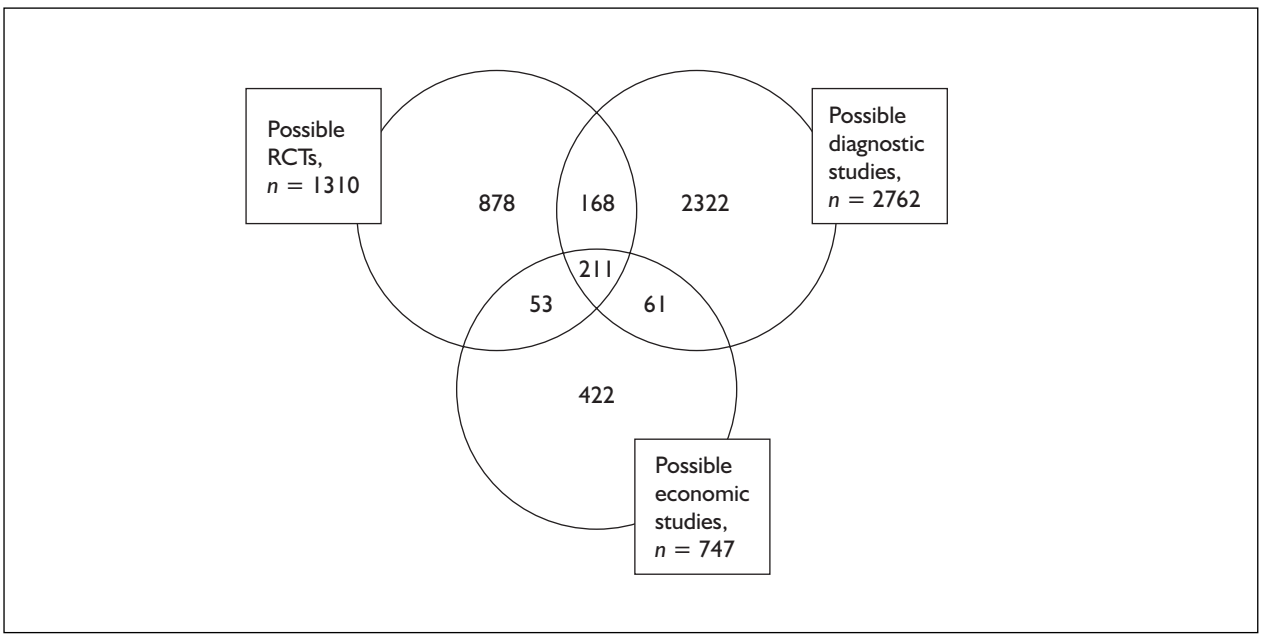


FIGURE 2 *Results of search strategy: number of 'possible' RCTs, diagnostic studies and economic studies*

Each of the studies was described individually, in a narrative fashion. All studies reported 2 × 2 diagnostic data and we calculated additional diagnostic outcomes (sensitivity, specificity, predictive values, likelihood ratios) as required. Where cells in 2 × 2 tables contained zero, a value of 0.5 was used in order to permit calculations. As each study addressed a different research question, data were not pooled. The numbers recruited according to wound aetiology were reported in all three studies (see Appendix 4, data extraction tables). A summary of the quality assessment of the diagnostic studies is given in Appendix 5. In one study, separate outcome data were provided on venous leg ulcers ($n = 7$), but the very small number of DFUs did not merit separate analysis ($n = 2$).[90] For the other two studies, data were reported for the overall sample of wounds of mixed aetiologies, without further breakdown. In terms of patient characteristics related to the DFU (type 1 or type 2 diabetes and presence of neuropathy/ischaemia), insufficient data were available from the papers to consider subgroup analyses according to these factors. One study reported the type of diabetes[90] and none of the studies reported numbers of patients with DFU who had neuropathy and/or ischaemia.

Review question 1: What is the diagnostic performance of clinical examination in the identification of infection in DFU? Gardner and colleagues (2001)[90]

In a cross-sectional study, people with chronic wounds of various aetiologies were recruited via four centres: an acute care veterans' facility, a long-term care veterans' facility, a mixed acute care and long-term care veterans' facility and a chronic wound clinic at a university medical centre. At three of the four study sites, only people with a white blood cell count of >1500 cells/mm^3 or a total lymphocyte count of >800 cells/mm^3, plus a platelet count of >125,000/mm were eligible for inclusion. People with wounds of arterial aetiology were excluded at all study sites. Of the overall sample of 36 participants, 19 had pressure ulcers, seven had venous leg ulcers, six had wounds from a secondary incision and two each had non-healing traumatic wounds and DFUs. Punch biopsy was the reference test and the index test consisted of the use of a clinical signs and symptoms checklist constructed from two other checklists. One of these checklists contained signs of infection that the study authors defined as 'classic': pain, erythema, oedema, heat and purulent exudate. The second checklist consisted of a list of signs and symptoms specific to secondary wounds proposed by other authors:[93] serous exudate plus concurrent inflammation, delayed healing, discoloration of granulation tissue, friable granulation tissue, pocketing of the wound base, foul odour and wound breakdown. The inter-rater reliability of the items on the checklist was assessed using wound observations made independently by the principal investigator and one of five specifically trained nurses, representing each study site (κ range from 0.53 to 1.00). The authors did not report outcomes for one clinical sign, pocketing of the wound base, as there was no agreement owing to non-occurrence of the sign within the study sample.[90] At the chronic wounds clinic, the biopsy was performed within 8 hours of data collection for clinical signs and symptoms; the time interval between tests was less than 1 hour for the other study sites (Gardner SE, University of Iowa School of Nursing: personal communication, 2003). Infection was defined as the presence of at least 10^5 organisms per gram of viable wound tissue, or wounds containing β-haemolytic *Streptococcus* at any level. Diagnostic measures were calculated for each individual clinical sign or symptom and verified against tissue biopsy findings. The results that follow are for the overall sample of wounds of various aetiologies. Explanations for the diagnostic outcomes used have been provided. Results are shown in *Table 4* and in Appendix 4.

Sensitivity and specificity are properties of a test that are concerned with the correct classification of people according to their disease status. It is assumed that the result of the reference test is correct, and therefore that a positive result from the reference test equates to presence of the disease and that a negative result denotes absence of the disease. Sensitivity can be defined as the proportion of participants with the target disease who have a positive result for the disease from the index test.[94] In this study, the highest sensitivity values were seen for two separate clinical signs, presence of friable granulation and delayed healing. They both correctly identified around 80% of patients with a wound infection. However, the respective specificity values were 76% and 64%, suggesting that the diagnostic performance of these two signs may be less than optimal. Although increasing pain and wound breakdown both had 100% specificity, they were associated with low sensitivity levels.

Predictive values are an estimate of the probability of disease, given the result of a test. They are determined by the prevalence of disease in the population being tested. Positive predictive value

TABLE 4 *Diagnostic outcomes for individual clinical signs and symptoms*[90]

Sign or symptom	Se (%)	Sp (%)	PPV	NPV	+LR	–LR
Increasing pain	36	100	100	78	18.18	0.64
Erythema	55	68	43	77	1.71	0.67
Oedema	64	72	50	82	2.27	0.50
Heat	18	84	33	70	1.14	0.97
Purulent exudate	18	64	18	64	0.51	1.28
Serous exudate plus concurrent inflammation	55	72	46	78	1.95	0.63
Delayed healing	81	64	50	89	2.27	0.28
Discoloration	64	56	39	78	1.45	0.65
Friable granulation	82	76	60	90	3.41	0.24
Foul odour	36	88	57	76	3.03	0.72
Wound breakdown	46	100	100	81	22.73	0.55

+/–LR, positive/negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

(PPV) is defined as the probability of disease in a patient with a positive index test result.[94] For the symptom of increasing pain and the sign of wound breakdown, the probability of patients with either of these clinical indicators having a wound infection was 100%, whereas the probability for those with purulent exudate was 18% (lowest value). Negative predictive value (NPV) is the probability of not having the disease when the test result is negative.[94] In this study, the probability of not having a wound infection in the absence of both friable granulation and delayed healing was around 90% (highest values), around 80% for increasing pain, oedema, serous exudate plus concurrent inflammation or discolouration, with the lowest value being 64% for purulent exudate.

Likelihood ratios (LRs) are another way of expressing the performance of a diagnostic test. Whereas sensitivity, specificity and predictive values use probability in their estimations, LRs are based on the use of odds. They estimate how many times more (or less) likely a test result is to be found in diseased compared with non-diseased participants.[94]

For this study, the range of values for positive LR (+LR) included 1.14 for heat and 22.73 for wound breakdown, meaning that, for example, wound breakdown is almost 23 times more likely to be observed in the presence of wound infection than in the absence of it. The +LR for increasing pain was around 18. The negative LR (–LRs) ranged from 0.97 for heat to 0.24 for friable granulation. These values gives odds of around 1:1.02 that absence of heat would occur in the presence of an infection compared with absence of infection, and odds of around 1:4.2 that absence of friable granulation would occur in the presence of an infection compared with absence of infection. A proposed 'rule of thumb' suggests that +LRs greater than 10 or –LRs less than 0.1 give convincing diagnostic evidence, and that values above five and below 0.2, respectively, provide strong diagnostic evidence.[88] Going by this, it seems that increasing pain and wound breakdown may be useful individually as diagnostic tests. However, these findings should be interpreted with caution owing to the small size of the study and the heterogeneity of the group recruited with respect to wound aetiology.

The LR values for one particular clinical sign, purulent exudate, merit special consideration (see data extraction table in Appendix 4, pp. 126–30). The calculated values are the opposite to what would normally be expected, that is, the +LR in this case is less than 1 (0.51), and the –LR is greater than 1 (1.28). This may be explained as follows. For the +LR, the ratio is derived from the very low sensitivity rate for this test (18%) and the relatively high number of false positives expressed as a proportion of the total without disease as verified by the reference standard. For the –LR the ratio is derived from the large proportion of false negatives relative to the total with disease and the specificity of 64%. These findings are as would be expected for a test that excludes disease as opposed to identifying it. The conclusion from these data is that purulent exudate is a particularly poor test for identifying wound infection, and that absence of this clinical sign is more likely to indicate infection than its presence. The values obtained for related diagnostic outcomes support this conclusion. In terms of sensitivity, only 18% of patients with a wound infection were correctly

identified with purulent exudate, and for specificity, 64% without a wound infection had absence of this clinical sign. In addition, the probability of patients with purulent exudate having a wound infection was 18% (PPV), and the probability of not having an infection in the absence of this sign was 64% (NPV). Another clinical sign that is noteworthy in this respect is the presence of heat around the wound. Heat had +LR and –LR values that were very close to one, indicating limited diagnostic usefulness (+LR 1.14, –LR 0.97). Other outcomes for heat were as follows: sensitivity 18%; specificity 84%; PPV 33%; and NPV 70%. Again, the small size of this study means that findings should be viewed with caution.

The author was contacted to request data stratified according to wound type. Data on sensitivity for clinical signs and symptoms for venous leg ulcers were provided (n = 7).[95] The values ranged from 100% for oedema or delayed healing to 25% for increasing pain, heat, serous exudate plus concurrent inflammation, discoloration or foul odour (see data extraction tables for the full range of values). The sensitivity for purulent exudate was 67%, somewhat higher than the value calculated for the overall sample.

A summary of the quality assessment of this study is given in Appendix 5. The selection criteria for patients were clearly described, all patients received both index and reference tests, the index test did not form part of the reference test, execution of both tests was described in sufficient detail to permit replication and there did not appear to be any uninterpretable test results or study withdrawals. Owing to the general scarcity of research in this area, it was unclear whether the reference test (tissue biopsy) would correctly classify wound infection. It was also unclear from the paper whether interpretation of test results was blind and whether the same clinical data would be available when test results were interpreted as would be available when the test is used in clinical practice. Standard practice may not involve examination of a gauze swab applied to the wound for 1 hour as an assessment for presence of exudate. For three of the four study sites, tissue biopsy was obtained less than 1 hour after clinical assessment (Gardner SE, University of Iowa School of Nursing, personal communication, 2003), and this would seem to be a short enough time interval to be confident that the infection status of the wound would not have changed between tests. However, the time lag was longer in the fourth site (8 hours) and it is possible that the infection status of the wound could have changed during this time. In terms of the spectrum composition (patient characteristics of the sample recruited for the study), the selection criteria used in three out of the four study sites (white blood cell count >1500 cells/mm^3 or total lymphocyte count >800 cells/mm^3; platelet count >125,000 mm) may have meant that the group recruited were not representative of the patients who would receive the test in clinical practice.

Summary

A wide range of values was seen for sensitivity, specificity and predictive values for the individual signs and symptoms. It is arguable that high sensitivity is most important in this context, in order to rule out disease, due to the potentially serious consequences of DFU infection. Interpretation of the derived LRs suggests that the signs and symptoms checklist is not a useful method of identifying infection in chronic wounds, with the possible exceptions of increasing pain and wound breakdown. The different values observed for the small subgroup of patients with venous leg ulcers relative to the whole sample may be due to chance or differential performance of the tool when used with specific wound types. Generalisability of findings is hindered owing to the participant eligibility criteria used and aspects of the method of assessment. Interpretation of study findings is further impeded by possible sources of bias and the current lack of information on an optimum reference standard.

Review question 2: What is the diagnostic performance of specimen acquisition techniques in the identification of infection in DFU?

Bill and colleagues (2001)[91]

Patients attending a university-based chronic wound centre were recruited to a cross-sectional study if they had a cutaneous wound at any body site, present for at least 6 months. Of the overall sample of 38 participants, 18 had pressure ulcers, 10 had DFUs and five each had venous leg ulcers and arterial ulcers. Punch biopsy taken from the centre of the wound was the reference test and wound swab with quantitative analysis was the index test. Tissue biopsy was carried out immediately after the wound swab was obtained. The authors defined soft tissue infection as the presence of more than >10^5 colony-forming units (CFUs) per gram of tissue for tissue biopsy and greater than >10^5 CFUs cm^2 for swab culture.[91]

Although the authors did not calculate diagnostic outcomes, they reported sufficient data to populate a 2 × 2 diagnostic table for the overall sample. From these data, the sensitivity, specificity, PPV, NPV, +LR and –LR for wound swab with respect to wound tissue biopsy as the reference standard were calculated.

The estimated sensitivity for wound swab was 79% and specificity was 60%, as verified by tissue biopsy. In terms of predictive values, PPV was 85% and NPV was 50%. The +LR was 1.96, meaning that a positive wound swab result is almost twice as likely to occur in people with a wound infection compared with those without an infection. The –LR was 0.36, giving odds of around 1:2.8 that a negative wound swab would occur in the presence of an infection compared with absence of infection. Going by the rule of thumb described previously, it seems that the wound swab as used in this evaluation is not a useful diagnostic test.

The authors were contacted and requested to provide 2 × 2 diagnostic data on the patients with DFUs, but data were unavailable.

The main issues around quality assessment (see Appendix 5) were lack of evidence as to whether tissue biopsy is a valid reference standard, no description of blind test verification and lack of clarity as to whether the same clinical data were available when test results were interpreted as would be available when the test is used in practice. On a positive note, the selection criteria and baseline characteristics of participants were clearly described, the time lag between tests was very short, patients were sampled consecutively and all patients received the reference test. The index test did not form part of the reference standard, and the execution of both tests was described in sufficient detail to permit replication. There did not appear to have been any uninterpretable tests or withdrawals from the study.

Summary

The sensitivity for wound swab was 79%, meaning that the swab would fail to detect approximately one in five wound infections. The derived LRs suggest that the wound swab is not a useful method of identifying infection in chronic wounds. Interpretation of study findings is impeded by possible sources of bias and the current lack of information on an optimum reference standard that should be used to verify the diagnostic performance of wound swab.

Review question 3: What is the diagnostic performance of different laboratory analysis techniques in the identification of infection in DFU?

Ratliff and Rodeheaver (2002)[92]

Patients attending a university-based wound care clinic were recruited if they had any type of cutaneous wound present at any body site for more than 6 months. Of the overall sample of 124 participants, 44 had pressure ulcers, 27 had ulcers due to venous insufficiency, 29 had neuropathic or diabetic ulcers, eight had lower extremity ulcers due to arterial disease and 16 had wounds due to other aetiologies (not described in the paper). The aim of this study was to assess the diagnostic performance of semi-quantitative analysis of wound swab using quantitative analysis as the reference standard. All patients had two wound swabs taken, using similar techniques and materials (calcium alginate-tipped swabs). Quantitative techniques for analysing specimens obtained from wound swabs involve identifying the type, and counting the numbers of microorganisms present. Semi-quantitative techniques entail classifying a level of bacterial growth by observing growth on four quadrants of an agar plate where each quadrant has been streaked in sequence using a sterile loop for each quadrant, thus making dilutions of the original streak on to each sequential quadrant. The greater the quantity of bacteria on the original swab, the more quadrants will display bacterial growth. In this study, the swab for quantitative analysis was obtained after the swab for semi-quantitative analysis; however, the time interval between acquisitions of the two specimens was not stated. Soft tissue infection was defined as the presence of at least 10^5 CFUs cm^2 for swab culture, derived from quantitative analysis.

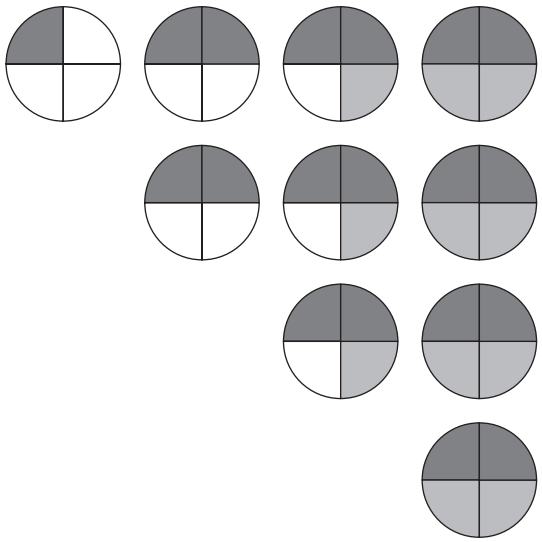
The authors presented 2 × 2 diagnostic data for different diagnostic thresholds of semi-quantitative and quantitative analyses (quantitative range from 10^2 to 10^7 CFUs cm^2 for swab culture). In the paper, sensitivity and specificity were reported for a reference standard level of 10^5 CFUs cm^2. We calculated additional diagnostic outcomes (predictive values and LRs) and also generated outcomes for a range of possible diagnostic thresholds for the semi-quantitative analysis, in each case using the stipulated reference standard level of 10^5 CFU cm^2 for the quantitative analysis. Referring to the spread of bacterial growth across quadrants of an agar plate, the range of diagnostic thresholds for semi-quantitative analyses are described and illustrated in *Box 2*.

A. Observed bacterial growth in any quadrant (Ql, or Q1 + Q2, Q1 + Q2 + Q3, or Q1 + Q2 + Q3 + Q4: the least strict definition of infection)

B. Observed bacterial growth in at least 2 quadrants: Q1 + Q2, or Q1 + Q2 + Q3, or Q1 + Q2 + Q3 + Q4

C. Observed bacterial growth in at least three quadrants: Q1 + Q2 + Q3, or Q1 + Q2 + Q3 + Q4 (the definition of infection used by the study authors)

D. Observed bacterial growth in all four quadrants: i.e. Q1 + Q2 + Q3 + Q4 (most strict definition of infection)



BOX 2 *Semi-quantitative descriptions of infection*

TABLE 5 *Diagnostic outcomes for semi-quantitative analysis of wound swab when different diagnostic thresholds (levels of growth) are used*

Level of growth[a]	Se (%)	Sp (%)	PPV (%)	NPV (%)	+LR	–LR
A	100	37	54	100	1.58	0.026
B	100	63	67	100	2.73	0.015
C	79	90	86	85	8.04	0.23
D	26	99	93	64	18.75	0.75

+/–LR, positive/negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.
[a] A, observed bacterial growth in quadrant I, quadrants I and II, quadrants I, II and III or quadrants I, II, III and IV; B, observed bacterial growth in quadrants I and II, quadrants I, II and III or quadrants I, II, III and IV; C, observed bacterial growth in quadrants I, II and III or quadrants I, II, III and IV; D, observed bacterial growth in quadrants I, II, III and IV.

The outcomes for the different levels of semi-quantitative analysis are given in *Table 5*.

As may be expected, sensitivity was higher with less stringent definitions of infection, whereas specificity decreased. As seen from *Table 5*, different values of sensitivity and specificity are derived when different diagnostic thresholds are used. When several different thresholds have been produced, these can be displayed on an ROC plot in order to help determine the optimum combination of sensitivity and specificity (and therefore the optimum diagnostic threshold to use). An ROC curve was generated for the four different levels of cut-off that were used for semi-quantitative analysis of wound swab (*Figure 3*). The true positive rate (sensitivity) is plotted against the false positive rate (1 – specificity). *Table 6* shows the coordinates used to plot the ROC curve. An uninformative test would be represented by a diagonal line sloping upwards from left to right across the graph. Coordinates appearing closest to the top left-hand corner of the graph indicate the most informative combination of sensitivity and specificity values, and therefore indicate the optimum diagnostic threshold to use.[88] According to these principles, it appears from this plot that threshold C is the most useful. However, as discussed in the original paper, it is necessary to consider the clinical implications of different rates of false positives and false negatives. For example, extrapolating from this study using the diagnostic threshold C (*Tables 5* and *6*), 21% of patients would have a false negative test result using semi-quantitative analysis and would experience a delay in receiving antimicrobial treatment. In addition, 10% of patients would have false positive results and would receive antimicrobial therapy unnecessarily.[92] Consideration of the effect of such rates on clinical outcomes and costs may help

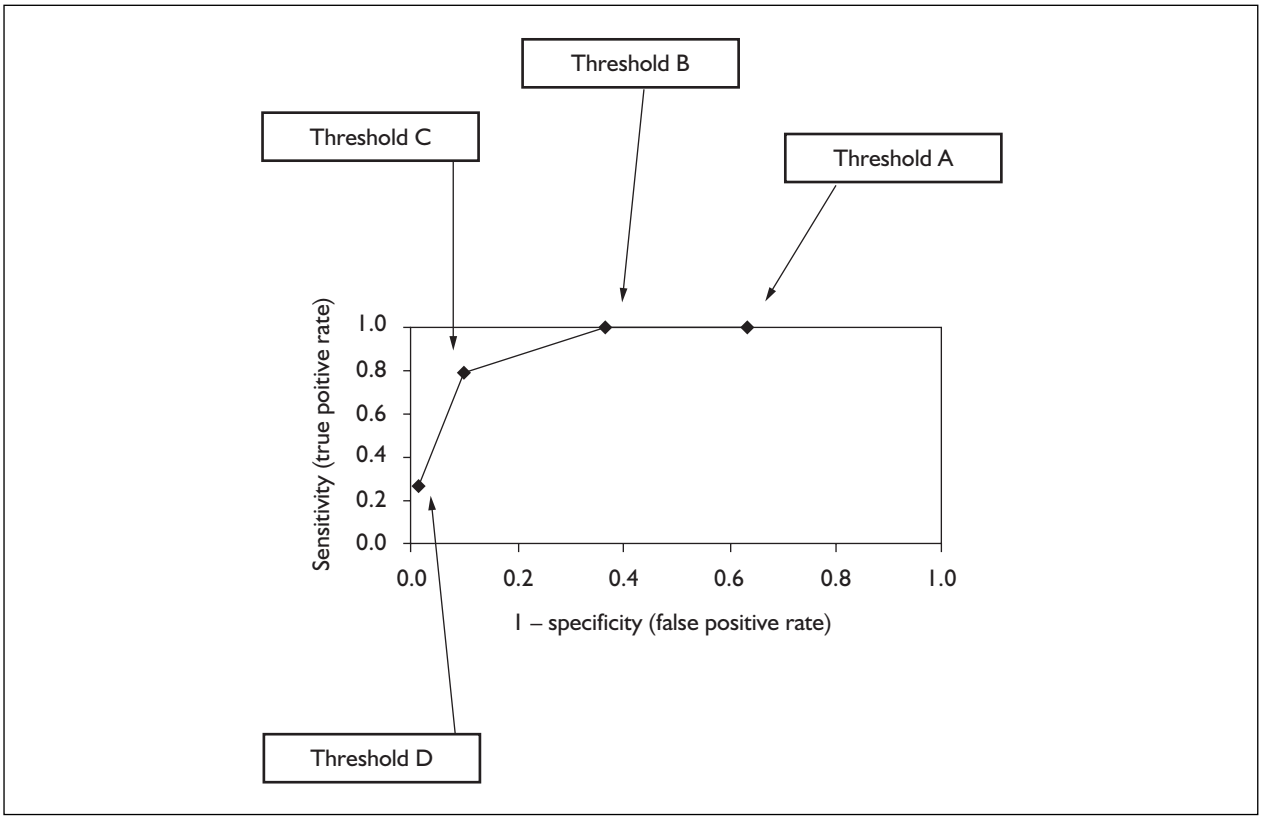


FIGURE 3 *ROC plot for detecting wound infection using semi-quantitative analysis of wound swab with reference to quantitative analysis of swab as the reference standard*

TABLE 6 *Coordinates used to plot the ROC curve*

Level of growth[a]	Sensitivity (true positive rate)	1 – Specificity (false positive rate)
A	1.000	0.634
B	1.000	0.366
C	0.792	0.099
D	0.264	0.014

[a] See *Table 5*.

clinicians to determine the optimum diagnostic threshold to use.

ROC curve plots enable the area under the curve to be estimated. This value is the probability of the diagnostic test correctly classifying a patient with or without an infection. The greater the area, the more accurate is the test, with perfect performance represented by a value of 1.0. A value of 0.5 represents an uninformative test.[96,97] For semi-quantitative analysis of wound swabs, the estimated area under the ROC curve was 0.92 [95% (CI) 0.87 to 0.97], meaning that the probability that cases were correctly classified was 92%.

In terms of predictive values, PPVs increased with the more strict criteria and NPVs decreased (*Table 5*). +LRs, an estimate of how many more times a positive test result is likely to be found in diseased people compared with non-diseased people, increased with increasing stringency of diagnostic criteria. According to the rule of thumb mentioned earlier for interpretation of +LRs, the strictest diagnostic criterion provided convincing diagnostic evidence (threshold D), the second strictest criterion provided strong diagnostic evidence (threshold C), whereas the values derived from the two least strict criteria were less informative (thresholds A and B). For –LRs, thresholds A and B (the less strict definitions of

infection) showed convincing diagnostic evidence, whereas for the two stricter definitions of infection (thresholds C and D), the values derived were not informative according to the rule of thumb. However, for diagnostic threshold C, the value approached usefulness (see *Table 5*).

A summary of the quality assessment for this study is given in Appendix 5. The patient selection criteria were clearly described and the spectrum of patients recruited appeared to be representative of those who would receive the test in clinical practice. All patients received both tests, the index test was not a component of the reference test, both tests were reported in sufficient detail to permit replication and there did not appear to be any uninterpretable results or study withdrawals. However, the time lag between tests was not stated. In addition, it was not clear whether the reference standard (quantitative analysis of wound swab) could correctly identify wound infection, whether blind interpretation of test results was performed or whether the same clinical data were available when test results were interpreted as would be likely to be available in clinical practice.

Summary

Findings suggest that semi-quantitative analysis may be a useful alternative to quantitative analysis, particularly for settings where the equipment and materials necessary for the latter are not available. Overall, threshold C gave the best diagnostic performance (see *Box 2*). Interpretation of study findings is hindered by possible sources of bias and the current lack of information on an optimum reference standard.

Effectiveness studies

Our searches identified 1903 citations, of which 163 were potentially relevant to questions 4 and 5, namely effectiveness/cost-effectiveness of microbiological analysis or antimicrobial agents.

Excluded studies

The 140 effectiveness studies that were thought to be potentially relevant to review questions 4 and 5, which were found to be ineligible after retrieval, are summarised in the excluded studies table in Appendix 6.

The reasons for exclusion were as follows: study not an RCT or CCT of an antimicrobial, $n = 98$; study did not report data for diabetic foot ulcers separately and <80% of patients had diabetic foot ulcers, $n = 40$. Two systematic reviews were identified in the search and these were handsearched for RCTs/CCTs.[98,99]

Review question 4: What impact does microbiological analysis have on therapy?

Included studies

We found no trials answering this question. Such studies would have compared a policy of taking a microbiological sample (e.g. swab) or not at the point at which a patient was deemed to have an infection and hence would have allowed us to evaluate the impact that microbiological analysis has on clinical outcomes.

Review question 5: What is the effectiveness and cost-effectiveness of management of infection in DFU?

Included studies

We identified 23 trials (21 RCTs and two CCTs), including 25 comparisons, addressing this question.

Quality of included studies

Details of study quality assessment are given in Appendix 5. The methodological quality of all included RCTs was assessed using the criteria reported in the Jadad five-point scale[85] and the allocation concealment criterion described by Schulz and colleagues.[86]

Results using the four assessment criteria are as follows. Nine studies reported appropriate methods of randomisation, 12 trials were simply described as 'randomised' and two allowed the patients to choose the groups to which they were allocated. Two studies reported an appropriate procedure for allocation concealment; in 17 studies it was unclear if the person randomising the participants was aware of the allocation, in two studies allocation was open and two studies were CCTs, in which patients chose their treatment. Three trials described appropriate double–blinding, five described the trial as double-blind, in 13 trials there was no information on double-blinding and in the two CCTs the patients and clinicians were not blinded. Thirteen studies reported the number and reason for withdrawals, nine studies did not report reasons for withdrawal by group and one reported no withdrawals.

Gough and colleagues[100] and Peterson and colleagues[101] both described appropriate methods for allocation concealment, described appropriate methods of generating the randomisation sequence, and both reported reasons and number

Grade	*Lesion*
0	No open lesions; may have deformity or cellulitis
1	Superficial diabetic ulcer (partial or full thickness)
2	Ulcer extension to ligament, tendon, joint capsule or deep fascia without abscess or osteomyelitis
3	Deep ulcer with abscess, osteomyelitis or joint sepsis
4	Gangrene localised to portion of forefoot or heel
5	Extensive gangrenous involvement of the entire foot

[a] *Source*: Frykberg.[104]

BOX 3 *Wagner ulcer classification system*[a]

Stage	Grade			
	0	1	2	3
A	Pre- or postulcerative lesion completely	Superficial wound, not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	With infection	With infection	With infection	With infection
C	With ischaemia	With ischaemia	With ischaemia	With ischaemia
D	With infection and ischaemia	With infection and ischaemia	With infection and ischaemia	With infection and ischaemia

BOX 4 *University of Texas San Antonio Diabetic Wound Classification System*

of withdrawals by study group. In addition, both stated they were double-blind, with the trial by Gough and colleagues[100]describing how this was achieved . Other trials may have been designed, performed and analysed to the highest standards but failed to report this in the study publication. Although these two trials were of high quality, the weight given to their findings is moderated by the fact that both are small (40 and 48 patients) and therefore underpowered.

Outcomes

There was a wide variation across studies of the outcome measures used. Twenty-one outcomes were reported and no single outcome was reported in all trials (*Table 7*). Adverse events, including death, were reported in 16 trials. Amputation was reported in 11 trials, clinical diagnosis of cure of infection in nine trials and proportion of ulcers healed in 11 trials. The large number of outcomes used and the lack of consistency in reporting outcomes mean that the data on effectiveness are difficult to synthesise.

The incidence of osteomyelitis, pain, ulcer recurrence, mobility, level of independence, number of hospital admissions or health-related quality of life were not reported in any of the included studies. A large number of outcomes, which we had not specified in the review protocol, were reported in the studies and these are identified in *Table 7* as shaded columns. Clinical cure of infection and the need for vascular reconstruction were not initially included in the review outcomes. As these outcomes were reported in nine and five trials, respectively, and we felt they may report clinically important outcomes, we decided, *post hoc*, to report these outcomes where they were available. If clinical assessments of infection status were found by the diagnostic reviews to be a valid indication of infection status (question 1), which was not the case, then this outcome would be a valid outcome measure. Vascular reconstruction may be seen as a procedure used to avert amputation, and therefore we felt that it may also provide clinically relevant information.

Population

There was wide variation in the types of patients recruited to the trials and the ulcer characteristics and settings are summarised in *Table 8*. There was no information on the severity of ulceration in 14 trials. One trial used its own ulcer grading system and the remainder (eight trials) used the Wagner classification system (*Box 3*)[102] or the University of Texas San Antonio Diabetic Wound Classification System (*Box 4*)[103] The latter classification system takes account of infection and ischaemia in addition to ulcer depth. Three trials stated that they included people with a grade 1 ulcer, six included grade 2 ulcers, four grade 3 ulcers and two grade 4 ulcers (as some trials

TABLE 7 *Outcome measures reported*[a]

Study ID	Limb outcomes			Infection outcomes										Ulcer healing outcomes				Organisation outcomes		
	Amputation	Vascular reconstruction	Required surgical debridement	Clinical cure of infection	Duration of antibiotic therapy	Eradication of pathogens	Required additional antibiotics	Cure of osteomyelitis	Bacteriology	Time to resolution of cellulitis	Time to clear swab	Proportion with resolution of cellulitis	Infection summary score	Proportion of ulcers healed	Time to healing	Area or volume change	Change in grade	Time to discharge	Costs	Adverse events
Intravenous interventions																				
Bouter (1996)[106]				×		×														×
Bradsher (1984)[43]						×			×											×
Erstad (1997)[107]	×	×		×		×														×
Grayson (1994)[44]	×	×		×	×	×													×	×
Lipsky (2004)[109]				×	×															×
Seidel (1991)[110]	×	×						×						×		×				×
Seidel (1993,1994)[111,112]	×													×						
Tan (1993)[108]				×		×														×
Oral interventions																				
Chantelau (1996)[74]						×										×				×
Lipsky (1990)[75]				×		×								×						×
Lipsky A[114]	×			×		×										×				×
Lipsky B[114]	×			×		×										×				×
Peterson (1989)[101]	×								×											×
Subcutaneous interventions																				
Gough (1997)[100]	×		×							×	×	×		×				×	×	×
Kastenbauer (2003)[118]												×	×	×		×	×			×
de Lalla (2001)[119]	×				×		×							×						×
Yonem (2001)[120]	×									×										
Topical interventions																				
Apelqvist (1995)[138]		×												×		×	×		×	
Marchina (1997)[123]														×						
Markevich (2000)[105]														×						
Rhaiem (1998)[124]														×	×				×	
Vandeputte (1996)[125]	×			×			×							×						×
Other interventions																				
Dwivedi (2000)[127]		×																		

[a] Shaded cells indicate outcomes listed in the protocol for this review as being relevant.

recruited patients with a range of ulcer severity, this total is greater than eight).

Four studies did not provide sufficient information to allow us to determine whether the patients had ulcers with established infection. Twelve studies stated that the ulcer was infected and seven evaluated antimicrobial agents on apparently uninfected ulcers.

Three studies did not report information on the site of treatment (inpatient or outpatient), 14 were

TABLE 8 *Characteristics of study settings and patient characteristics*

Study	Setting	Ulcer grade	Infected
Bouter (1996)[106]	IP	Wagner grade 2, 3 or 4	Y
Bradsher (1984)[43]	IP	No information	Y
de Lalla (2001)[119]	IP	Wagner grades 3 and 4	Y
Erstad (1997)[107]	IP	Used own grading system – most were grade 2 and 3 – cellulitis + skin break or cellulitis + deep ulcer or cellulitis and puncture plus suspected osteomyelitis	Y
Gough 1997[100]	IP	No data on grade	Y
Grayson (1994)[44]	IP	No data on grade but did provide data on baseline coma	Y
Kastenbauer (2003)[118]	IP	Wagner grade 2 or 3	Y
Lipsky (2004)[109]	IP	No data on grade	Y
Peterson (1989)[101]	IP	No data on grade	Y
Rhaiem (1998)[124]	IP	No data on grade	N
Seidel (1991)[110] (CCT)	IP	No data on grade, 12/40 had osteomyelitis	Unclear
Seidel (1993,1994)[111,112]	IP	No data on grade,	Unclear
Tan (1993)[108]	IP	No data on grade	Y
Yonem (2001)[120]	IP	Wagner grade 2 or less	Y
Markevich (2000)[105]	IP	Grade 2 and 3	N
Apelqvist (1996)[122]	OP	Wagner grade 1 or 2	N
Dwivedi (2000)[127]	OP	No data on grade	Unclear
Lipsky A[114]	OP	No data on grade	N
Lipsky B[114]	OP	No data on grade	N
Lipsky (1990)[75]	OP	No data on grade	Y
Chantelau (1996)[74]	OP + IP	Grade 1A to 2A (Texas)	Unclear
Marchina (1997)[123]	Unclear	1st or 2nd degree (not defined)	N
Vandeputte (1996)[125]	Unclear	No data on grade	N

IP, inpatient; OP, outpatient; Y, yes; N, no.

conducted on inpatients, five on outpatients and one on both inpatients and outpatients. The site of treatment was related to the presence of established infection (*Table 8*). Eleven studies of established infection in ulcers were undertaken in hospital inpatients and only one treated people with infected ulcers as outpatients.[75] One study apparently reported treatment of people without established infection as inpatients.[105] There were two studies in which the setting was not clear and an additional four studies in which the status of the patient regarding ulcer infection was not clear. Therefore, it is not clear whether the relationship between infection status and site of treatment is clear cut.

Interventions and comparisons

A number of intervention types were included in this review: intravenous, oral, subcutaneous, topical and other methods. The 'other' group included, for example, studies comparing oral and topical administration methods with a topical intervention, or where there were mixed methods of administration.

Comparisons of methods of administration included studies of intravenous versus intravenous administration, oral versus oral, topical versus topical, oral versus topical and subcutaneous versus standard care or placebo. The various comparisons made are summarised in *Table 9*.

Owing to the heterogeneity in intervention and outcomes, it was not possible to undertake any meta-analyses.

Effectiveness of intravenous interventions

Eight studies are included in this group. Four trials made straight comparisons between intravenous regimens,[44,106–108] one compared two regimens in which therapy started as intravenous and was changed to oral as the patient's condition improved,[109] two trials (three reports) compared two different methods of infusion of antibiotics (retrograde venous perfusion and regular intravenous infusion)[110–112] and one compared an intravenous antibiotic with a comparator given either IV or intramuscularly.[43]

TABLE 9 *Comparisons made in included studies.*

	i.v	Oral	Topical	Placebo	Standard care
i.v. antibiotics	1. Bouter[106] 2. Erstad[107] 3. Grayson[44] 4. Lipsky[109] 5. Seidel[110] 6. Seidel[111] 7. Tan[108]				
Oral antibiotics		1. Lipsky[75] 2. Peterson[101]	1. Lipsky A[114] 2. Lipsky B[114]	1. Chantelau[74]	
Subcutaneous growth factors				1. Gough[174] 2. Kastenbauer[118]	1. de Lalla[119] 2. Yonem[120]
Topical antimicrobial			1. Apelqvist[122] 2. Marchina[123] 3. Markevich[105] 4. Vandeputte[125]		1. Rhaiem[124] (sugar vs standard care)
Other antimicrobial agents	1. Bradsher[43] (i.v. versus either i.v. or i.m.)		1. Rhaiem[124] (sugar vs antibiotics)		1. Dwivedi [127]

We found no trials comparing an intravenous antibiotic with a placebo. We found no studies comparing an intravenous antibiotic against an oral, topical or subcutaneous intervention.

All comparisons were unique and each featured two active treatment groups. In seven trials more than one antibiotic was used, for example ampicillin and sulbactam (A/S) or imipenem and cilastatin (I/C); only Bradsher and Snow made a simple comparison of two single antibiotics, ceftriaxone versus cefazolin.[43] A/S was a comparator in three trials,[44,107,109] I/C was a comparator in two trials[44,106] and linezolid,[109] piperacillin and clindamycin (P/C),[106] piperacillin and tazobactam[108] and ticarcillin and clavulanate (T/C)[108] were each used in one trial. One comparison of two methods of infusion used piperacillin and gentamicin[110] and the other used piperacillin and netilmycin.[111,112]
The trial results are summarised in *Table 10*. Further details on each trial are provided in the data extraction tables in *Appendix 4*.

Description of the studies

Bouter and colleagues (1996)[106]
Bouter and colleagues[106] compared I/C with P/C administered intravenously in 46 hospitalised patients (mean age 71.4 years) with DFUs whose ankle/brachial index was at least 0.45. The antibiotic treatment period was a minimum of 10 days and the mean duration of therapy was 23–24 days. All patients underwent bed rest and thrombolytic therapy. Foot infections were identified as polymicrobial in more than half of the cases. There was no statistically significant difference in the numbers of people with clinical 'cure' (defined as the disappearance of initial infection) between the two groups: 4/22 (18%) with I/C and 6/24(25%) with P/C (RR 1.38, 95% CI 0.48 to 4.11). There was no statistically significant difference in the prevalence of 'bacterial eradication', 9/22 (41%) for I/C and 16/24 (67%) for P/C (RR 1.63, 95% CI 0.94 to 3.02). The incidence of adverse events was statistically significantly higher in the P/C group (50%) than in the I/C group (19%) (RR 3.67, 95% CI 1.33 to 11.13), with diarrhoea being the single most frequently reported event. The trial was underpowered, however, so it was unable to detect all but massive differences in effectiveness as statistically significant.

Bradsher and Snow (1984)[43]
Bradsher and Snow compared cefazolin given intravenously with ceftriaxone administered either intravenously or intramuscularly in 84 inpatients with suspected skin and soft tissue infection, of whom 20 had suppurative DFUs.[43] Baseline information on demographics and bacteriology is presented for the whole study population, including people with cellulitis, abscess, thrombophlebitis, pressure ulceration and surgical wound infection. Results for the people with DFUs

TABLE 10 *Summary of comparisons, outcomes and results from effectiveness studies*

Study	Comparison A Comparison B	Outcome	Data	RR, 95% CI (dichotomous outcomes) *Mean difference, 95% CI (continuous outcomes)*
Intravenous interventions				
Bouter (1996)[106]	Imipenem/cilastatin Piperacillin/clindamycin	Clinical 'cure' (disappearance of initial infection)	I/C 4/22 (18%) P/C 6/24 (25%)	RR 1.38 95% CI 0.48 to 4.11
	Imipenem/cilastatin Piperacillin/clindamycin	'Bacterial eradication'	I/C 9/22 (41%) P/C 16/24 (67%)	RR 1.63 95% CI 0.94 to 3.02
Bradsher (1984)[43]	Cefazolin Ceftriaxone	'Infection eliminated' at follow-up	I/C 4/10 (40%) P/C 6/10 (40%)	RR 1.5 95% CI 0.60 to 3.74
Erstad (1997)[107]	Ampicillin/sulbactam Cefoxitin	Any amputation	A/S 8/18 (44%) C 8/18 (44%)	RR 1.0 95% CI 0.48 to 2.09
	Ampicillin/sulbactam Cefoxitin	Clinical 'cure' (resolution of signs and symptoms of infection)	A/S 1/18 (6%) C 7/18 (39%)	RR 0.14 95% CI 0.02 to 0.76
	Ampicillin/sulbactam Cefoxitin	Adverse events	A/S 7/18 (39%) C 6/18 (33%)	RR 1.17 95% CI 0.5 to 2.8
Grayson (1994)[44]	Ampicillin/sulbactam Imipenem/cilastatin	Total number of amputations	A/S 33/48 (69%) I/C 28/48 (58%)	RR 0.85 95% CI 0.62 to 1.15
	Ampicillin/sulbactam Imipenem/cilastatin	Clinical 'cure' (resolution of soft tissue infection) at the end of treatment	A/S 28/48 (58%) I/C group 29/48 (60%)	RR 1.04 95% CI 0.74 to 1.45
	Ampicillin/sulbactam Imipenem/cilastatin	Clinical 'cure of infection' rates at final follow-up	A/S 27/48 (56%) I/C 33/48 (69%)	RR 1.22 95% CI 0.89 to 1.7
	Ampicillin/sulbactam Imipenem/cilastatin	Adverse events	A/S 16/48 (33%) I/C 17/48 (35%)	
Lipsky (2004)[109]	Linezolid (i.v. or oral) Ampicillin/sulbactam or amoxicillin clavulanate	Clinical cure rate (resolution of all clinical signs and symptoms and a healing wound after 5 days of therapy)	Linezolid 69% (131/190) AS/AC 63% (57/93)	RR 0.92 95% CI 0.76 to 1.09
	Linezolid (i.v. or oral) Ampicillin/sulbactam or amoxicillin/clavulanate	Mean total duration of therapy required	Linezolid mean 17.2 days AS/AC mean 16.5 days	*Difference = –0.7 days* *95% CI –2.66 to 1.26*
	Linezolid (IV or oral) Ampicillin/sulbactam or amoxicillin/clavulanate	Duration of treatment with i.v. antibiotics	Linezolid mean 7.8 days AS/AC mean 10.4 days	*Mean difference 2.6 days* *95% CI 1.22 to 3.98*
	Linezolid (i.v. or oral) Ampicillin/sulbactam or amoxicillin clavulanate	Withdrawing from the study due to an adverse event	Linezolid, *n* = 18 (7.5%) AS/AC *n* = 4 (3.3%)	RR 2.24 95% CI 0.82 to 6.24

continued

TABLE 10 *Summary of comparisons, outcomes and results from effectiveness studies (cont'd)*

Study	Comparison A Comparison B	Outcome	Data	RR, 95% CI (dichotomous outcomes) *Mean difference, 95% CI (continuous outcomes)*
Seidel (1991)[110]	i.v. antibiotics RVP infusions of antibiotics	People requiring amputation due to underlying osteomyelitis	i.v. 4/20 RVP 0/20	RR 9 Haldane approximation 95% CI 0.52 to 157
	i.v. antibiotics RVP infusions of antibiotics	Number of ulcers healed	i.v. 0/20 RVP 6/20	RR 0.077 Haldane approximation 95% CI 0.005 to 1.28
	i.v. antibiotics RVP infusions of antibiotics	'Resolved' osteomyelitis	i.v. 0/7 RVP 4/5	RR 0.083 Haldane approximation 95% CI 0.005 to 1.27
Seidel (1993, 1994)[111,112]	i.v. antibiotics RVP infusions of antibiotics	Amputation rate	i.v. 4/21; 19% RVP 3/24; 12.5%	RR 1.52 95% CI 0.42 to 5.57
	i.v. antibiotics RVP infusions of antibiotics	Ulcers healed	i.v. 3/21 (14%) RVP 8/24 (33%)	RR 0.43 95% CI 0.13 to 1.28
Tan (1993)[108]	Piperacillin/tazobactam (P/T) Ticarcillin/clavulanate	Clinical 'cure' (defined as recovery from infection)	Per protocol analysis (PPA) P/T 56% (9/16): T/C 86% (6/7) Intention to treat analysis (ITTA) P/T 29% (9/31) T/C 33% (6/18)	PPA: RR 0.66 95% CI 0.37 to 1.26 PPA ITTA: RR 0.87 95% CI 0.39 to 2.07 if all missing data assumed to equal 'failed to achieve a cure'
Oral interventions				
Chantelau (1996)[74]	Amoxycillin+clavulanic acid (Augmentin®) Placebo	Healing rates	A/C 6/22 (27%) Placebo 10/22 (45%)	RR 1.67 95% CI 0.76 to 3.83
	Amoxycillin+clavulanic acid (Augmentin®) Placebo	Absence of microbes in deep swab wound cultures taken at completion of the study	A/C 7/22, 32% Placebo 6/22, 27%	RR 0.86 95% CI 0.35 to 2.09
Lipsky (1990)[75]	Clindamycin hydrochloride (Cleocin) Cephalexin (Keflex)	Infection 'cure' rate (signs and symptoms resolved)	Per protocol analysis (PPA) Clindamycin 21/27 (78%) Cepahlexin 21/29 (72%)	RR 0.93 95% CI 0.67 to 1.29
	Clindamycin hydrochloride (Cleocin) Cephalexin (Keflex)	Ulcers healing	Per protocol analysis Clindamycin 10/27 (37%) Cephalexin 9/29 (31%)	RR 0.83 95% CI 0.4 to 1.73

continued

TABLE 10 *Summary of comparisons, outcomes and results from effectiveness studies (cont'd)*

Study	Comparison A Comparison B	Outcome	Data	RR, 95% CI (dichotomous outcomes) *Mean difference, 95% CI (continuous outcomes)*
	Clindamycin hydrochloride (Cleocin) Cephalexin (Keflex)	Eradication of bacterial pathogens	Per protocol analysis Clindamycin 20/26 (77%) Cephalexin 20/29 (69%)	RR 0.9 95% CI 0.63 to 1.26
	Clindamycin hydrochloride (Cleocin) Cephalexin (Keflex)	Adverse events	Clindamycin 1 Cephalexin 2	RR 2.0 95% CI 0.28 to 14.8
Lipsky A[114]	Pexiganan cream Ofloxacin	Number of amputations	Pexiganan 6/246 (2.4%) Ofloxacin 4/247 (1.6%)	RR 1.5 95% CI 0.46 to 4.92
	Pexiganan cream Ofloxacin	Clinical 'cure' rates (no further signs or symptoms of infection) at day 10	Pexiganan 63/243 (26%) Ofloxacin 67/240 (28%)	RR 1.08 95% CI 0.81 to 1.45
	Pexiganan cream Ofloxacin	'Microbiologically resolved infection' at final follow-up	Pexiganan 75/185 (40%) Ofloxacin 84/193 (44%)	RR 1.07 95% CI 0.85 to 1.36
	Pexiganan cream Ofloxacin	Adverse events leading to patient withdrawal	Pexiganan 28/247 (11%) Ofloxacin 23/246 (9%)	RR 0.82 95% CI 0.49 to 1.38
	Pexiganan cream Ofloxacin	Serious adverse events	Pexiganan 28/247 (11.3%) Ofloxacin 20/246 (8.1%)	RR 0.72 95% CI 0.42 to 1.23
Lipsky B[114]	Pexiganan cream Ofloxacin	Clinical 'cure' rates (defined above) at day 10	Pexiganan 34/171 Ofloxacin 34/171	RR 1.0 95% CI
	Pexiganan cream Ofloxacin	Infection 'resolved'	Pexiganan 44 (26%) Ofloxacin 30 (18%)	RR 0.68 95% CI 0.45 to 1.02 ITT principle: assume sample size = 171 for each group and all missing patients not cured
	Pexiganan cream Ofloxacin	Adverse events leading to patient withdrawal	Pexiganan 16/171 (9%) Ofloxacin 15/171 (9%)	RR 0.94 95% CI 0.48 to 1.81
Peterson (1989)[101]	750 mg 1000 mg twice daily ciprofloxacin	Number of amputations	750 mg, *n* = 4/24 (17%) 1000 mg, *n* = 6/24 (25%)	RR 1.5 95% CI 0.51 to 4.49
	750 mg 1000 mg twice daily ciprofloxacin	Adverse events which resulted in discontinuation of the drug	2 in 1000 mg group	RR 5 Haldane approximation 95% CI 0.25 to 99

continued

TABLE 10 *Summary of comparisons, outcomes and results from effectiveness studies (cont'd)*

Study	Comparison A Comparison B	Outcome	Data	RR, 95% CI (dichotomous outcomes) *Mean difference, 95% CI (continuous outcomes)*
Sub-cutaneous interventions				
Gough (1997)[100]	G-CSF Placebo (saline)	Toe amputation	G-CSF 0/20 Placebo 2/20	RR 5 Haldane approximation 95% CI 0.3 to 98
	G-CSF Placebo (saline)	Ulcer healed	G-CSF 4/20 (20%) Placebo, 0/20	RR 9 Haldane approximation 95% CI 0.5 to 157
Kastenbauer (2003)[118]	G-CSF Placebo (saline)	Healed at day 10	G-CSF 0/20 Control 2/20 (10%)	RR 5 Haldane approximation 95% CI 0.3 to 98
de Lalla (2001)[119]	G-CSF Standard care	Amputation rate	G-CSF group 3/20 (15%) Standard care 9/20 (45%)	RR 0.33 95% CI 0.11 to 0.95
	G-CSF Standard care	'Cured' or had a stable ulcer at 6 months	G-CSF 13/16 Standard care 15/20	RR 0.92 95% CI 0.63 to 1.38
Yonem (2001)[120]	G-CSF Standard care	Proportion of patients requiring amputation	G-CSF 2/15 (13%) Standard care 3/15 (20%)	RR 0.67 95% CI 0.15 to 2.95
Topical interventions				
Apelqvist (1995)[138]	Cadexomer iodine ointment Gentamicin or streptodornase/ streptokinase or dry saline gauze	Number of patients who required surgical intervention	Standard treatment 5/18 (28%) Cadexomer iodine 3/17 (18%)	RR for surgery 0.64 95% CI 0.19 to 2.07
	Cadexomer iodine ointment Gentamicin or streptodornase/ streptokinase or dry saline gauze	Ulcer healed	Cadexomer iodine 5/17 (29%) Standard care 2/18 (11%)	RR 2.65 95% CI 0.68 to 10.89
Marchina (1997)[123]	Antiseptic spray (content not described) 2% eosin and 0.3% chloroxylenol spray	Completely healed at 15 days	Antiseptic spray 50% Eosin/chloroxylenol 82%	NA
Markevich (2000)[105]	Larvae Hydrogel	Ulcer healing	Larval therapy 5/70 (7.1%) Hydrogel 2/70 (2.9%)	RR 2.5 95% CI 0.58 to 10.9

continued

TABLE 10 *Summary of comparisons, outcomes and results from effectiveness studies (cont'd)*

Study	Comparison A Comparison B	Outcome	Data	RR, 95% CI (dichotomous outcomes) *Mean difference, 95% CI (continuous outcomes)*
Rhaiem (1998)[124]	Systemic antibiotics Sugar	Healing rate	Systemic antibiotics 16/40 (40%) Sugar 8/16 (50%)	RR 1.25 95% CI 0.64 to 2.23
	Sugar dressings Standard dressings Used with systemic antibiotics		Sugar dressings 11/24 (46%) Standard dressings 16/40 (40%)	RR 0.87 95% CI 0.5 to 1.59
	Systemic antibiotics No antibiotics Also sugar dressings	Ulcer healing	Systemic antibiotics 11/24 No antibiotics 8/16	RR 1.09 95% CI 0.55 to 2.07
Vandeputte (1996)[125]	Hydrogel dressing Gauze and chlorhexidine	Necessity for amputation (one or more toes)	Hydrogel 1/15 (7%) Chlorhexidine 5/14 (36%)	RR 5.4 95% CI 0.98 to 32.7
	Hydrogel dressing Gauze and chlorhexidine	Ulcers healed	Hydrogel 14/15 (93%) Chlorhexidine 5/14 (36%)	RR 2.61 95% CI 1.45 to 5.76
	Hydrogel dressing Gauze and chlorhexidine	Incidence of infection	Hydrogel group 1/15 (7%) Chlorhexidine 7/14 (50%)	RR 7.5 95% CI 1.47 to 44.1
	Hydrogel dressing Gauze and chlorhexidine	Systemic/local antibiotics/required	Hydrogel 1/15 (7%) Chlorhexidine 14/14 (100%)	RR 0.067 95% CI 0.01 to 0.31
Other interventions				
Dwivedi (2000)[127]	Ayurvedic medicine vs standard care	Required surgery	Active 16% Standard care 30%	NA

NA, not available.

are reported as 'bacteriological response'. Six people in the ceftriaxone group and four in the cefazolin group were described as having their 'infection eliminated' at follow-up (RR 1.5, 95% CI 0.60 to 3.74). The study reported the outcomes of amputation, the need for other surgical procedures (such as incision and drainage or debridement) and adverse events for all patients combined (not stratified by patient type), hence it is difficult to determine whether these could be generalised to the DFU population.

Erstad and colleagues (1997)[107]
Erstad and colleagues compared A/S versus cefoxitin, both administered intravenously, in a double-blind RCT.[107] Thirty-six hospitalised patients with at least a Wagner grade 1 diabetic foot infection were treated for a minimum of 5 days, with initial follow-up at 2 weeks post-hospital discharge and again at 1 year. Thirty-three of the 36 (92%) had open ulcers. Following treatment, similar proportions of patients had had amputations in each study group, i.e. 8/18 (44%). The RR for any amputation was 1.0 (95% CI 0.48 to 2.09). There was also no statistically significant difference between the levels of amputation in the two groups, i.e. number of either toe amputations or toe and ray amputations. Some 33% (6/18) of people allocated to cefoxitin had a toe amputation, whereas of those receiving A/S, 17% (3/18) had a toe amputation, RR for toe amputation 0.5 (95% CI 0.15 to 1.55). In the cefoxitin group, the proportion of people with combined toe and ray amputations was 5.5% (1/18), in the A/S group it was 22% (4/18) (RR 4.0, 95% CI 0.68 to 25.4). There was no statistically significant difference in the rate of revascularisation in the cefoxitin (4/18; 22%) or A/S groups (2/18; 11%) (RR 0.5, 95% CI 0.12 to 2.06). More people in the cefoxitin group (7/18; 39%) were reported as having a clinical 'cure' (defined as complete resolution of presenting signs and symptoms of infection) than in the A/S group (1/18; 6%) (RR 0.14, 95% CI 0.02 to 0.76).

The report also describes an outcome in which 'cure' and 'improved' patients were pooled (without stating why this outcome was used), and found no statistically significant difference in the proportions with this outcome (15/18; 83% A/S; 16/18; 89% cefoxitin). A per protocol analysis of the rate of eradication of bacterial pathogens found no statistically significant difference between groups: 8/11 (73%) in the cefoxitin group and 6/6 (100%) in the A/S group (RR 1.38, 95% CI 0.7 to 2.17). An intention-to-treat analysis for eradication of bacterial pathogens also found no statistically significant difference between groups: 8/18 (44%) in the cefoxitin group and 6/18 (33%) in the A/S group (RR 0.75, 95% CI 0.32 to 1.69). Adverse events, all described as gastrointestinal in nature, were reported in 6/18 (33%) of the cefoxitin group and 7/18 (39%) of the A/S group (RR 1.17, 95% CI 0.5 to 2.8). The trial was underpowered (for all outcomes) in terms of its ability to detect clinically important differences that were statistically significant.

Grayson and colleagues (1994)[44]
A double-blind RCT with 93 patients (96 infections) compared the intravenous administration of A/S with I/C in hospital inpatients with diabetes who had a limb-threatening infection of the feet or legs, of whom 92% (88) had a foot ulcer.[44] A 'limb-threatening infection of the feet or legs' was defined as (as least) the presence of cellulitis, with or without ulceration or purulent discharge. The treatment period averaged 14 days and follow-up was at 1 year. All patients had bed rest, surgical drainage and debridement of infected ulcers and necrotic tissue. There were no statistically significant differences between the A/S and the I/C groups for the total number of amputations [33/48 (69%) A/S versus 28/48 (58%) I/C; RR 0.85, 95% CI 0.62 to 1.15; *NB* the denominator is number of infections rather than patients]. There was no statistically significant difference in the number of infections requiring vascular reconstruction in the A/S (7/48; 15%) or I/C (15/48; 31%) groups (RR 2.14, 95% CI 0.99 to 4.76). There was no statistically significant difference in the rate of clinical 'cure' (defined as the resolution of soft tissue infection) at the end of treatment in the A/S group (28/48, 58%) or I/C group (29/48, 60%) (RR 1.04, 95% CI 0.74 to 1.45). Similarly, at final follow-up, clinical 'cure of infection' rates in the two groups were not statistically significantly different: 27/48 in A/S (56%) and 33/48 (69%) in I/C (RR 1.22, 95% CI 0.89 to 1.7).

The authors reported that there was no statistically significant difference in the number of doses or duration of antibiotic therapy; however, there were insufficient data provided in the paper to allow us to calculate the mean differences or CIs. They also reported no statistically significant difference in the eradication of bacterial pathogens at day 5 [17/48 (35%) in A/S versus 20/48 (42%) in I/C] and at end of therapy (32/48 in A/S versus 36/48 in I/C) (RR 1.125, 95% CI 0.87 to 1.46). The proportion of patients with any adverse events was 33% (16/48) in A/S versus 35% (17/48) in I/C, with half of these described as 'significant' (for example, diarrhoea, rash, nausea or seizure).

The trial was underpowered in terms of its ability to detect clinically important differences as statistically different for all reported outcomes. As there were no statistically significant clinical differences between study groups, the concurrent economic analysis compared only the costs of primary, secondary treatment and hospital bed costs using 1994 US dollar prices.[113] The results revealed that the mean total treatment cost was lower (by $3000 per patient; $14,000 versus $17,000) with A/S. Sensitivity analysis showed that the I/C treatment regimen would need to be 30% more effective than A/S in order to reach the criteria for cost-effectiveness as defined in this study (i.e. absolute risk difference for probability of success of around 30%). For the outcomes amputation, cure of infection at end of treatment and cure of infection at final follow-up, and vascular reconstruction the difference in event rates excludes the value where I/C would be 30% more effective than A/S, but larger trials are needed to increase the precision of the estimates of effectiveness and cost-effectiveness.

Using a matrix of cost-effectiveness[87,89] in which costs and effectiveness outcomes are integrated, then A/S is preferred over I/C as there is no evidence of difference in effectiveness with reduced costs, corresponding to cell H of the table in *Box 1*.

Lipsky and colleagues (2004)[109]

An open-label, multi-centre RCT compared linezolid (intravenously or orally administered) versus A/S (intravenously) or amoxicillin and clavulanate (A/C) (orally) in 361 patients with diabetic foot infections, of whom 78% had foot ulcers.[109] This study was identified by contact with experts and was published in 2004. The method of administration was switched (from intravenous to oral) at the investigators' discretion and therapy was continued on both an inpatient and outpatient basis for at least 7 days, but no more than 28 days. Data on 283 people with DFUs were presented separately. Vancomycin was added to the A/S or A/C regimen where necessary for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and all patients received wound dressings, but not topical antimicrobial treatments. Investigators could administer aztreonam 1–2 g intravenously, every 8–12 hours, if required for the treatment of Gram-negative pathogens if the allocated intervention was not effective against them. Wounds with callus or necrotic material were sharply debrided.

There was no statistically significant difference in the overall clinical cure rate (resolution of all clinical signs and symptoms and a healing wound after 5 days of therapy) for those with infected ulcers, 69% (131/190) in linezolid and 61% (57/93) in A/S or A/C (RR 0.92, 95% CI 0.76 to 1.09). There was no statistically significant difference between groups in the mean total duration of therapy required [mean 17.2 days, standard deviation (SD) 7.9 in linezolid versus mean 16.5 days (SD 7.9), difference –0.7 days, 95% CI –2.66 to 1.26]. Patients were treated with intravenous antibiotics for longer in the A/S or A/C group [mean 10.4 days (SD 5.7)] than the linezolid group [mean 7.8 days (SD 5.5); mean difference 2.6 days, 95% CI 1.22 to 3.98]. A number of adverse events were reported, including diarrhoea, nausea, anaemia, thrombocytopenia, vomiting, decreased appetite and dyspepsia. Adverse events were reported for the whole study population (of whom 78% had ulcers). There were 64 events in 241 people with linezolid, of whom 18 patients (7.5%) discontinued therapy because of the event, and 12 events in 120 people in the A/S or A/C group, of whom four (3.3%) discontinued therapy. As patients could experience more than one adverse event, and the study does not report the number of people in each group who experienced any event, we have calculated the RR of withdrawing from the study due to an adverse event (RR 2.24, 95% CI 0.82 to 6.24).

Seidel and colleagues (1991)[110]

Seidel and colleagues conducted two CCTs in which male inpatients with diabetic neuropathic plantar ulcers chose either conventional intravenous or retrograde venous perfusion (RVP), that is, injection into a dorsal vein during arterial occlusion. In the first study, the RVP group had one RVP infusion daily of gentamicin, buflomedil, dexamethasone, heparin and lignocaine in isotonic saline. This group also had an intramuscular injection of gentamicin, a long-acting buflomedil tablet and three intravenous infusions of piperacillin.[110] The standard infusion technique group had three infusions per day of piperacillin, gentamicin, buflomedil and heparin in dextran. Both groups received the same regimen of local antibacterial therapy. Results included the number of people requiring amputation due to underlying osteomyelitis [0/20 in the the RVP and 4/20 in the intravenous group; RR 9 (Haldane approximation used to avoid error in the χ^2 tests if cell contains 0; it involves adding 0.5 to all of the cells of contingency table), 95% CI 0.52 to 157], although there were 10% more cases of osteomyelitis in this group at baseline, and the number of ulcers healed (6/20 in RVP and 0/20 intravenous; RR 0.077, 95% CI 0.005 to 1.28).

They also reported mean reduction in ulcer size (55% in RVP, 7.5% in intravenous), but the report does not specify whether the accompanying figures (±8 and ±3.6) represent the standard error, SD or range and therefore the CI for the difference cannot be calculated. Of those with osteomyelitis, 4/5 in the RVP group and 0/7 in the intravenous group had 'resolved' [RR 0.083 (Haldane approximation), 95% CI 0.005 to 1.27]. Note that none of the outcomes were assessed blind to the study group. The authors state that bacterial analysis was amongst the outcome measures, but no data were presented. A number of adverse events were noted in the RVP group, including petechiae (tiny broken blood vessels: 6/20), pain from arterial occlusion (5/20), haemorrhage (4/20) and stasis dermatitis (3/20).

Seidel and colleagues (1993)[111] and (1994)[112]
In a later study, the same group compared intravenous and RVP administration of antibiotics in 45 male inpatients with diabetic neuropathic plantar ulcers (DNPUs) over a 10-day period.[111,112] People in the intravenous group had three infusions per day of netilmycin, buflomedil, heparin, rheomacrodex and dexamethasone, plus twice daily piperacillin (intravenous). The RVP group had once daily infusions of netilmycin, buflomedil, dexamethasone, lidocaine and heparin, plus an evening injection (intravascular) of netilmycin, a buflomedil tablet, and twice daily piperacillin (intravenous). All patients received similar wound cleansing and dressing, along with dietary and medical interventions for diabetes. There was no statistically significant difference in the amputation rate in the two groups [3/24 (12.5%) in RVP versus 4/21 (19%) in intravenous: RR 1.52, 95% CI 0.42 to 5.57]. The number of ulcers healed was not statistically significantly different in the two groups: 8/24 (33%) RVP and 3/21 (14%) intravenous (RR 0.43, 95% CI 0.13 to 1.28). The study was underpowered to detect clinically important differences in amputation rate or healing as statistically significant.

Tan and colleagues (1993)[108]
Tan and colleagues reported a double-blind multi-centre RCT in 251 patients of whom 49 had foot ulcers.[108] Results for people with DFUs were reported separately. They compared piperacillin and tazobactam (P/T) with T/C over a minimum of 5 days in hospitalised patients with complicated skin/skin structure infections. Treatment continued for at least 48 hours following the resolution of signs and symptoms, followed by early (24–72 hours) and late monitoring (10–14 days) after treatment completion. The number of evaluable patients with foot ulcers (of whom the majority were diabetic; the exact proportion was not reported in the paper) was 16/31 (52%) receiving P/T and 7/18 (39%) receiving T/C. Reasons for non-evaluability are only available for the complete treatment group, but these were failure to meet diagnostic criteria for infection 10%, no baseline pathogen 10%, inadequate clinical follow-up 9%, prestudy antibiotic 7%, concomitant infection 6%, resistant pathogen at baseline 4% and 'other reasons' 11%; 55% of those recruited were therefore non-evaluable. All patients underwent surgical debridement or drainage as part of their management programme. The mean duration of therapy was 8–9 days. Results for those evaluable patients with foot ulcers showed no significant difference in the rate of achieving a clinical 'cure' (defined as recovery from infection) between the T/C and P/T groups. A per protocol analysis reported that the 'cure of infection' rate with T/C was 86% (6/7) and 56% (9/16) with P/T (RR 0.66, 95% CI 0.37 to 1.26). An intention-to-treat analysis of 'cure of infection' rates found that 33% (6/18) with T/C and 29% (9/31) with P/T had this outcome (if all persons in whom data are missing are assumed to have failed to achieve a cure of infection) (RR 0.87, 95% CI 0.39 to 2.07). The high proportion of missing data from ulcer patients means that these results must be treated with caution.

The trial was underpowered in terms of its ability to detect clinically important differences in outcomes amongst people with foot ulcers as statistically significant. The proportion of patients experiencing at least one adverse event was reported for all patients in the trial (of whom 20% had an ulcer) and was 42% in both groups, with gastrointestinal events (diarrhoea) being a frequent cause (11% of people in each group had a gastrointestinal adverse event).

Summary
The eight trials of intravenous antibiotics do not provide robust evidence of the superiority of any particular antibiotic regimen over any other, or whether retrograde perfusion is superior to standard infusion techniques. Erstad colleagues found that cefoxitin was better than A/S for an outcome of clinical cure (in a trial described as double-blind), but there was insufficient evidence regarding differences for outcomes of amputation, revascularisation, bacterial eradication or adverse events.[107] Bouter and colleagues found that I/C was associated with fewer adverse events probably related to the trial drug than P/C, although there was insufficient evidence of any differences in

effectiveness outcomes of bacterial eradication of pathogens or clinical cure.[106] Lipsky and colleagues reported that the length of treatment with A/S or A/C was greater than that with linezolid, although there was insufficient evidence regarding any differences in clinical cure of infection rates or adverse events.[109] None of the six RCTs in this group reported that their method of allocation was masked so that the person performing the randomisation was unaware of the schedule, but three of them described themselves as double blind.[44,107,108] Four of the six RCTs described appropriate methods of randomisation.[43,44,106,108] Only the study by Tan and colleagues[108] reported that it was double-blind and reported an appropriate method to generate the allocation sequence.

The two CCTs by Seidel and colleagues allowed patients to choose their mode of therapy – conventional intravenous or RVP therapy. Insufficient information is presented on the characteristics to allow one to examine any differences in patient selection at the outset.[110–112] Even if the two groups were well matched at the outset for characteristics known to be prognostic, the groups may not be comparable for unknown prognostic variables. In addition, those patients who chose the novel treatment may differ from those who chose conventional therapy.

Effectiveness of oral interventions

Five studies are included in this group. One study compared oral antibiotics with placebo,[74] two compared different orally administered antibiotics[75,101] and two studies compared a topical intervention with oral antibiotics (reported in one document).[114] We found no studies that compared an oral intervention with an intravenous or subcutaneous intervention.

Description of the studies

Chantelau and colleagues (1996)[74]

Chantelau and colleagues[74] compared oral A/C (Augmentin®) with an identical placebo over a 20-day period in a double-blind RCT involving 44 patients with foot lesions graded 1A to 2A using the Texas classification system (*Box 4*).[115] All patients received mechanical debridement, wound cleansing, dressing and pressure relief. The authors state that there was no statistically significant difference in mean reduction in ulcer size, but insufficient data were reported to allow calculation of effect size or CIs. There was no statistically significant difference between healing rates [6/22 (27%) in A/C and 10/22 (45%) in placebo; RR 1.67, 95% CI 0.76 to 3.83]. In addition, there was no difference in the numbers of people whose deep swab wound cultures taken at completion of the study showed absence of microbes [7/22, (32%) in A/C versus 6/22 (27%) in placebo; RR 0.86, 95% CI 0.35 to 2.09] or isolates [4/22 (18%) in A/C versus 1/22 (5%) in placebo; RR 0.25, 95% CI 0.04 to 1.51] at the end of the study. Diarrhoea occurred in only one patient (active intervention group) and this was resolved without withdrawal from the study. Five other patients were withdrawn at the beginning of the trial owing to non-compliance or bacteria unresponsive to the antibiotic. It was not clear whether these patients were included in the analysis. The trial was underpowered in terms of its ability to detect clinically important differences as statistically significant.

Lipsky and colleagues (1990)[75]

Lipsky and colleagues compared orally administered clindamycin hydrochloride (Cleocin) with cephalexin (Keflex) in an RCT amongst 60 male outpatients with diabetes (data reported on 56 people).[75] Treatment was over 2 weeks, with 3 months of follow-up. Patients with clinically infected lower extremity lesions were included in the study, with 89% and 93% in the respective study groups having an ulcer. All patients had lesions cleansed and debrided at the initial evaluation and this was followed by instructions for self-care. There was no statistically significant difference in the infection 'cure' rate (where all signs and symptoms resolved), in a per protocol analysis, between clindamycin and cephalexin group [21/27 (78%) in clindamycin versus 21/29 (72%) in cepahlexin; RR 0.93, 95% CI 0.67 to 1.29]. There was no statistically significant difference in the proportion of ulcers healing in a per protocol analysis between clindamycin, 10/27 (37%) and cephalexin, 9/29 (31%) (RR 0.83, 95% CI 0.4 to 1.73). Results for the eradication of bacterial pathogens, using per protocol results, showed a similar cure rate in each of the study groups [20/26 (77%) for clindamycin and 20/29 (69%) for cephalexin; RR 0.9, 95% CI 0.63 to 1.26]. Adverse events were noted in only three patients (one in the clindamycin group and two in the cephalexin group; RR 2.0, 95% CI 0.28 to 14.8), presenting as mild diarrhoea and nausea. The trial was underpowered in terms of its ability to detect clinically important differences as statistically significant.

Lipsky and colleagues (unpublished) A[114] and B[114]

Two trials by Lipsky and colleagues compared an oral and a topical intervention. These were identified by contact with experts. The comparison

was of topically applied pexiganan cream (Locilex®) with ofloxacin (orally) over a 14–28-day period with follow-up at 2 weeks after treatment had ended.[114,116] The authors describe pexiganan cream as a broad-spectrum antimicrobial agent, structurally related to frog skin peptides. This product has not been licensed for use.[117] These double-blind RCTs recruited outpatients with a DFU in whom there were no signs of extensive cellulitis, exposure of bone/tendon or fever. All patients were offered debridement and standard dressings. The authors present results at three time points (day 10, end of treatment and follow-up), in 10 populations (including intention-to-treat, per protocol, intention-to-treat microbiology and per protocol microbiology). The primary outcome was 'clinical outcome at day 10 in an evaluable population'. Other outcomes included clinical outcome at three time points, microbiological outcome at three time points, therapeutic response at three time points, wound score, wound infection score, wound depth, absolute and relative wound area reduction (mean and median) and eradication of pathogens present at baseline. The large number of outcomes (which may have been necessary for the submission to the Federal Drug Administration committee) may have led to a Type I error, that is, concluding that there is a statistically significant difference when none exists.

Lipsky and colleagues (unpublished) A[114]
Results from the first of these studies (493 participants) revealed no statistically significant difference between the number of amputations in the pexiganan group [4/247 (1.6%)] and the ofloxacin group [6/246 (2.4%)] (RR 1.5, 95% CI 0.46 to 4.92).

There was no statistically significant difference between the clinical 'cure' rates (defined as no further signs or symptoms of infection) at day 10 [63/243 (26%) in pexiganan and 67/240 (28%) in ofloxacin (RR 1.08, 95% CI 0.81 to 1.45], at end of treatment, [133/247 (54%) pexiganan and 150/246 (61%) in ofloxacin (RR 1.13, 95% CI 0.97 to 1.32] and at final follow-up [136/243 (56%) in pexiganan and 156/240 (65%) in ofloxacin (RR 1.16, 95% CI 1.00 to 1.34)]. The mean reduction in wound area was similar in the two groups, namely 93.4 mm^2 area reduction in pexiganan and 96 mm^2 area reduction in ofloxacin, but insufficient data were provided to allow the calculation of CIs. At final follow-up, the numbers of people with an outcome described as 'microbiologically resolved infection' were 75/185 (40%) in pexiganan and 84/193 (44%) in ofloxacin (RR 1.07, 95% CI 0.85 to 1.36). There were a similar number of adverse events leading to patient withdrawal from the study in pexiganan [28/247 (11%)] and ofloxacin [23/246 (9%)] (RR 0.82, 95% CI 0.49 to 1.38), the most frequent causes being diarrhoea, nausea and pain. The incidence of serious adverse events such as cellulitis, infection or osteomyelitis was not statistically significantly different in pexiganan [28/247 (11.3%)] from ofloxacin [20/246 (8.1%)] (RR 0.72, 95% CI 0.42 to 1.23).

Lipsky and colleagues (unpublished) B[114]
The second study compared pexiganan and ofloxacin in 342 patients. There was no statistically significant difference in the number of people who had an amputation: 7/171 (4%) in the pexiganan group and 3/171 (2%) in the ofloxacin group (RR 0.43, 95% CI 0.12 to 1.49). Clinical 'cure' rates (defined above) were not statistically significantly different at day 10 (34/171 in pexiganan and 34/171; RR 1.0, 95% CI 0.65 to 1.53) or at end of treatment (84/171 in pexiganan and 80/171; RR 1.05, 95% CI 0.84 to 1.31). The mean reduction in wound area was 129 mm^2 in pexiganan and 142.6 mm^2 in ofloxacin, but insufficient data were provided to allow the calculation of CIs. Microbiological response at 10 days was analysed both per protocol and intention-to-treat. Forty-four patients (26%) had an outcome of 'resolved' in pexiganan and 30 (18%) were 'resolved' in ofloxacin. If one assumes that the sample size for this analysis is 171 for each group and that none of the patients for whom data are missing had a microbiological 'cure', the RR of 'resolved' is 0.68 (95% CI 0.45 to 1.02) using an intention-to-treat principle. This result is sensitive to the assumption that all missing data represented failures as the authors present the microbiological cure as occurring in 44/138 (32%) pexiganan and 30/140 (21%) ofloxacin (RR 0.67, 95% CI 0.45 to 0.99). There was no statistically significant difference in the proportion of patients classified as 'resolved' in the two groups at end of treatment, that is, 53/171 (31%) in pexiganan and 59/171 (34%) in ofloxacin (RR 1.11, 95% CI 0.82 to 1.51) or follow-up, 50/171 (29%) in pexiganan and 61/171 (36%) in ofloxacin (RR 1.22, 95% CI 0.89 to 1.66). Adverse events leading to patient withdrawal in this study involved similar proportions of patients in each group: 16/171 (9%) from the pexiganan group and 15/171 (9%) from the ofloxacin group (RR 0.94, 95% CI 0.48 to 1.81). The causes of adverse events were the same as in the larger Lipsky pexiganan study (described above). Serious adverse events were observed in 22/171 (13%)

pexiganan and 19/171 (11%) ofloxacin (RR for serious adverse events 0.86, 95% CI 0.49 to 1.52).

We did not pool the data from the Lipsky studies as there was differential drop-out from the two arms (ofloxacin and pexiganan) and we felt that this may have been misleading to use the per protocol data available. Given that this treatment is not licensed for use currently, we did not pursue acquiring the data from the study sponsors.

Peterson and colleagues (1989)[101]

Peterson and colleagues compared the effectiveness of orally administered ciprofloxacin in an RCT in which 48 inpatients with lower extremity DFUs were given different doses (750 or 1000 mg twice daily) of ciprofloxacin, with follow-up at 12 months.[101] Patients with osteomyelitis were treated for 3 months and those with cellulitis for 3 weeks. All patients received local wound care, comprising debridement, wound cleansing, dressing and pressure relief. Data were available on 45 patients. There was no statistically significant difference in the number of amputations between the 750 and 1000 mg dose groups: 4/24 (17%) in the 750 mg and 6/24 (25%) in the 1000 mg group (RR 1.5, 95% CI 0.51 to 4.49). A number of adverse events occurred, of which two resulted in discontinuation of the drug [both in the high-dosage group; RR 5 (Haldane approximation), 95% CI 0.25 to 99]. Six patients in the high-dose group and two in the low-dose groups experienced non-serious adverse events such as chemical abnormalities (increased blood urea nitrogen or serum creatinine levels) thought to be associated with the treatment (RR 0.33, 95% CI 0.08 to 1.28). The trial was underpowered.

Summary

Five studies compared oral interventions, with only the two unpublished studies by Lipsky (reported in the same document) comparing the same interventions (topical pexiganan and oral ofloxacin) more than once.[114] There is insufficient evidence from the studies to recommend any particular oral antimicrobial: none of the studies reported significant difference on any outcomes, although trials by Chantelau and colleagues,[74] Lipsky and colleagues[75] and Peterson and colleagues[101] were so small that they were unlikely to detect clinically important differences in outcomes as statistically significant. The two large (unpublished) trials by Lipsky with 835 patients, in which an oral antibiotic was compared with an antimicrobial cream, found no difference in outcomes in per protocol analyses.[114]

Peterson and colleagues described allocation concealment, an appropriate method of randomisation (by the pharmacy).[101] The other four trials did not make it clear whether allocation was concealed. Both trials of pexiganan and ofloxacin were described as double-blind.[114]

Effectiveness of subcutaneous interventions

Four included studies evaluated subcutaneous administration of recombinant human granulocyte-colony stimulating factor (rhG-CSF, also known as filgrastim; Neupogen®) in addition to standard care versus placebo plus standard care,[100,118] or standard care alone.[119,120] Granulocyte colony-stimulating factor (G-CSF) is an endogenous haemopoietic growth factor that induces terminal differentiation and release of neutrophils from the bone marrow. There were no studies comparing any subcutaneous interventions with an intravenous, oral or topical treatment.

Description of the studies

Gough and colleagues (1997)[100]

The double-blind RCT by Gough and colleagues compared a subcutaneous injection of G-CSF with a placebo (saline solution) in 40 inpatients with a DFU with extensive cellulitis (the majority occurring in the forefoot) over a 7-day period.[100] G-CSF dosage was initially 5 µg/kg/day (daily for 2 days), and was then titrated against the patient's neutrophil count, reduced to 2.5 µg/kg/day (daily for 2 days), and then given on alternate days (up to 7 days). All patients received an intravenous combination of four antibiotics (ceftazidime, amoxycillin, flucloxacillin and metronidazole), appropriate glycaemic control, foam dressings and podiatric treatment. Two patients in the placebo group underwent toe amputation compared with none in the G-CSF group [RR for amputation 5 (Haldane approximation), 95% CI 0.3 to 98]. Two patients in the placebo group required extensive debridement under anaesthesia, compared with none in the G-CSF group [RR for debridement 5 (Haldane approximation), 95% CI 0.3 to 98]. The study is underpowered to detect clinically important differences in debridement or amputation outcomes as statistically significant. The median time to resolution of cellulitis was 7 days in the G-CSF group (range 5–20) and 12 days in the placebo group (range 5–93). The median time to negative swab was 4 days in the G-CSF group (range 4–10) versus 8 days in the placebo group (range 5–93), and although there were insufficient data available to allow us to calculate the CIs for the difference in time, the authors stated that the difference was statistically

significant. There was no statistically significant difference in the number of people whose ulcer healed in the two groups; 4/20 (20%) patients in the G-CSF group healed their ulcer, whereas no patients in the placebo group had a healed ulcer, but this difference was not statistically significant [RR 9 (Haldane approximation), 95% CI 0.5 to 157]. People in the G-CSF group were more likely to have resolution of cellulitis at day 7 than the placebo group [11/20 (55%) versus 4/20 (20%), RR 2.75, 95% CI 1.1 to 7.3]. The median time to hospital discharge was reportedly lower in the G-CSF group than the placebo group [10 days (range 7–31) versus 17.5 1 days (range 9–100)] but insufficient data were provided to calculate the CI for the difference. The authors state that this difference is statistically significant at the conventional 95% level. There was leucocytosis amongst some G-CSF patients (at day 7 the patients receiving G-CSF had higher counts of lymphocytes and monocytes than patients in the control group). The median dose of G-CSF required over the study period was 302 µg/day (range 200–440).

It is noteworthy that the median duration of ulcers prior to trial entry in the G-CSF group was 21 days (range 2–1278) compared with 39.5 days (range 2–1825) in the placebo group, indicating that the G-CSF group was more likely to heal from baseline as the randomisation of a small number of participants had failed to distribute ulcers of long duration equally between the two groups. An economic analysis of G-CSF versus placebo was undertaken by Edmonds and colleagues,[121] using the resource use data from the first 28 patients (of 40), in the Gough trial,[100] from a hospital rather than a societal perspective. A decision tree model was built to estimate the mean treatment cost for each group. They estimated that the mean cost savings associated with G-CSF over placebo were £2666. Sensitivity analysis was undertaken to examine the effect of changing assumptions about the patient type, probability distribution, unit cost and duration of hospital stay on cost-effectiveness. They identified that the savings ranged from £155 to £3129 when patients with vascular problems and/or tissue necrosis were excluded from the study. The authors pointed out that the results of the economic analysis should be interpreted with caution as the two groups were treated differently after randomisation; more patients in the placebo group had a vascular problem than in the G-CSF group (seven versus four) and these required more costly diagnostic tests and interventions. The results therefore need to be confirmed in a large RCT.

Given that there is no clear evidence of difference in effectiveness, but lower costs associated with G-CSF, then in an economic analysis G-CSF is preferred – corresponding to cell H of the cost-effectiveness matrix in *Box 1*.[87,89]

Kastenbauer and colleagues (2003)[118]

A second study in this group[118] was a single (patient)-blinded RCT that compared the same dose of G-CSF as Gough and Colleagues[100] with a placebo (sterile saline solution). Thirty-seven hospital inpatients with a DFU (Wagner grade 2 or 3) were treated over a 10-day period.[102] All patients maintained bed rest and received the same standard wound care, including debridement. Intravenous antibiotics (clindamycin and ciprofloxacin) were administered, followed by oral antibiotics where necessary. Daily clinical observations were supplemented by the calculation of an Infection Summary Score (no information was provided on validation of this scale). Healing data were presented as changes in Wagner grade, reduction in volume, resolution of cellulitis and complete ulcer healing. All five of the grade 3 ulcers from the GCSF group and all three of the grade 3 ulcers in the placebo group progressed to grade 2 ulcers by day 10. There were similar reductions in ulcer volume in the control group (125 µl) and the G-CSF group (120 µl), but there was no data on the variance to allow the calculation of CIs of the change. Furthermore, the groups were not comparable at baseline for ulcer volumes (203 versus 358 µl) and this may have biased the result. The proportion of patients with unresolved cellulitis at day 10 showed a greater number in the active intervention group (approximately 27% versus 17%, data derived from graph). There was no statistically significant difference in the proportion of patients achieving complete healing at day 10: 10% (2/20) in the control group versus none in the G-CSF group [RR 5 (Haldane approximation), 95% CI 0.3 to 98]. Adverse events of worsened liver function and skin efflorescence were noted in two patients in the G-CSF group. The trial was underpowered to detect clinically important differences as statistically significant.

de Lalla and colleagues (2001)[119]

An RCT by de Lalla and colleagues compared conventional treatment (local treatment plus systemic antibiotic therapy) and additional subcutaneously administered G-CSF with conventional treatment alone in 40 hospitalised patients with a DFU over 21 days.[119] Follow-up was carried out at 9 weeks and 6 months. All patients had either Wagner grade 3 or 4 ulcer (described as limb threatening) and all received local

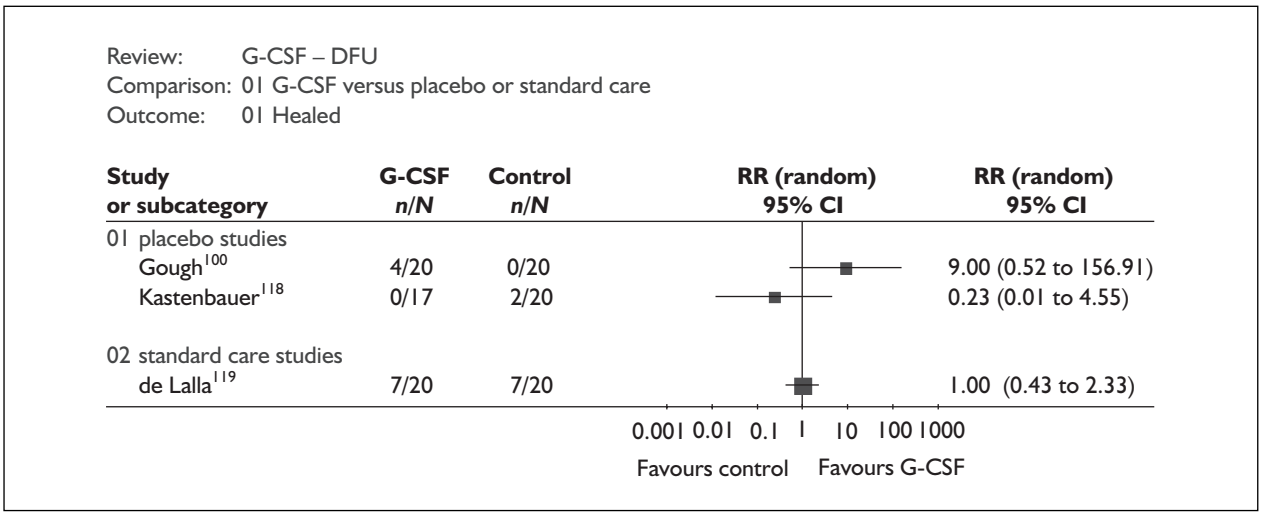


FIGURE 4 *Forest plot of GCSF versus placebo or standard care for ulcer healing*

treatment and empirical antibiotic therapy (intravenous or oral ciprofloxacin and clindamycin) where necessary. The amputation rate was statistically significantly higher in the conventional treatment group at the end of treatment [9/20 (45%)] compared with the G-CSF group [3/20 (15%)] (RR 0.33, 95% CI 0.11 to 0.95). There was no statistically significant difference in the number of major amputations performed in the conventional treatment group [2/20 (10%) conventionally treated versus 0/20 (0%) in the G-CSF group] [RR 0.2 (Haldane approximation) 95% CI 0.01 to 3.9]. There was no reported difference between groups in the proportion of ulcers 'cured' (complete closure of the ulcer without signs of underlying bone infection) at 21 days (none healed in both groups) or 9 weeks, as 7/20 (35%) healed in both groups (RR 1.0, 95% CI 0.43 to 2.3). At 6 months 13/16 people in the GCSF group were either 'cured' or had a stable ulcer (four lost to follow-up) compared with 15/20 in the control group (RR 0.92, 95% CI 0.63 to 1.38).

There was no statistically significant difference in the mean/median duration of antibiotic therapy in the G-CSF group (58.7 days, SD 23.7) or the standard care group (68.9 days, SD 29.2), mean difference 10.2 days (95% CI –6.3 to 26.7 days). In addition, there were no statistically significant differences between groups in terms of the proportion of patients requiring oral/antibiotic therapy during the trial period [11/20 (55%) versus 13/20 (65%), RR for oral therapy required in standard care 1.18, 95% CI 0.7 to 2.04]. There was no statistically significant difference between groups in terms of proportion of patients requiring adjustments to empirical therapy [9/20 (45%) in standard care versus. 7/20 (35%) in G-CSF, RR 0.78, 95% CI 0.36 to 1.65]. The authors reported that there were no adverse events associated with G-CSF but two patients in this group required a reduced dose of G-CSF owing to an elevated neutrophil count.

Yonem and colleagues (2001)[120]

Yonem and colleagues evaluated subcutaneous G-CSF against 'standard' local wound care in 30 people; all patients received intravenous ciprofloxacin and metronidazole.[120] The setting and length of treatment were not reported. All participants had either pedal cellulitis or a foot lesion (Wagner grade 2 or less) secondary to diabetes mellitus and were placed on a daily multiple-dose injection of short-acting insulin. There was no statistically significant difference in the proportion of patients requiring amputation [3/15 (20%) in standard care versus 2/15 (13%) in the G-CSF group; RR 0.67, 95% CI 0.15 to 2.95]. The number of days to resolution of infection was 22.3 in standard care (SD 1.7) and 23.6 in G-CSF (SD 1.8) (mean difference 1.3 days; 95% CI 0.05 to 2.55). This trial was underpowered to detect clinically important outcomes such as amputation as statistically significant. Adverse events were not reported.

Three of the four G-CSF studies reported the rate of compete ulcer healing, and *Figure 4* summarises the results for the three studies.

Three of the four G-CSF studies reported amputation rates, and *Figure 5* summarises the results for these three studies.

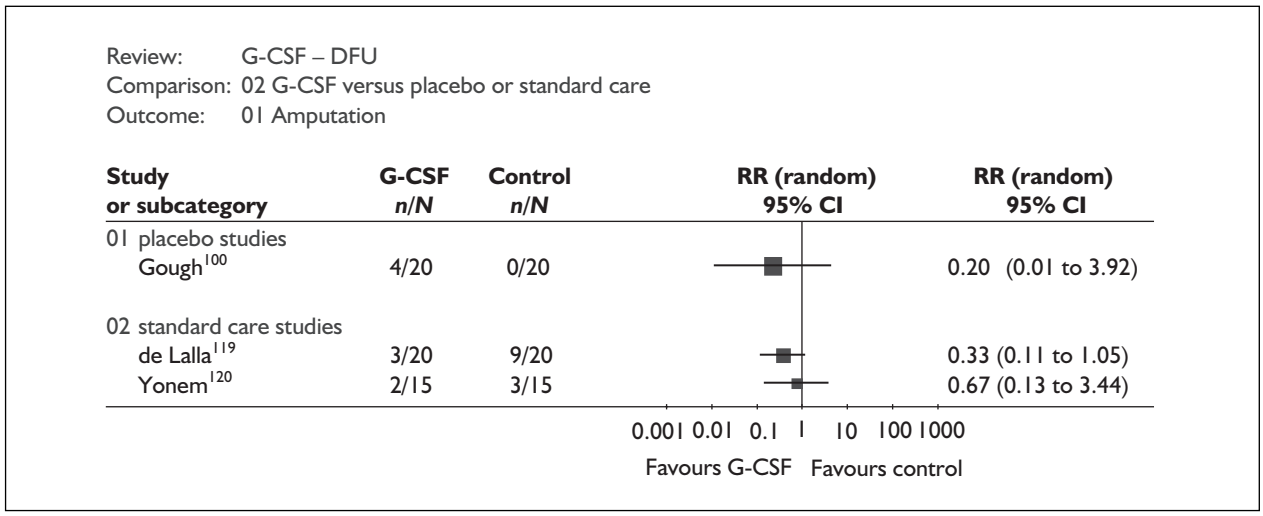


FIGURE 5 *Forest plot of G-CSF versus placebo or standard care for amputation*

Given that one study by Yonem and colleagues[120] did not report ulcer healing outcomes and the potential methodological and clinical heterogeneity, we decided not to combine the healing results in a meta-analysis. A similar approach was used for the amputation results as one study (Kastenbauer and colleagues[118]) did not report amputation rates.

Summary

There is no reliable evidence that G-CSF is associated with reduced amputation rates or increased ulcer healing but the trials are too small (total of 147 participants) to exclude the possibility that there is a clinically important effect.

A cost study[121] of one of the trials[100] suggested lower treatment costs associated with G-CSF but the authors stated that this finding should be treated with caution as it was based on a retrospective analysis of 28 patients from the 40 in the original trial, and the two groups received different concurrent treatments such as surgery post-randomisation.

Effectiveness of topical interventions

Five eligible studies compared different topical preparations[105,122–125]

Description of the studies

Apelqvist and colleagues (1996)[122,126]

An open RCT by Apelqvist and colleagues was conducted in Sweden with 41 outpatients (with Wagner grade 1 or 2 diabetic foot ulcer) over a 12-week period.[122,126] The study compared topically applied cadexomer iodine ointment (Iodosorb®) with a standard topical treatment consisting of gentamicin (Garamycin®), streptodornase/streptokinase (Varidase®) or dry saline gauze (Mesalt®). The authors described cadexomer iodine ointment as a highly fluid-absorbing, antibacterial agent. All patients were offered oral antibiotics (ciprofloxacin, cephalosporin, metronidazole, clindamycin) if necessary, along with saline dressing, a paraffin gauze and special footwear where appropriate. Outcomes are given on 35 patients as no data are presented on five patients from the cadexomer iodine group and one from the standard care group. There was no statistically significant difference in the number of patients who required surgical intervention in the standard treatment [(5/18 28%)] or the chlorhexidine group [3/17 18%)] (RR for surgery 0.64, 95% CI 0.19 to 2.07). There was no statistically significant difference between the proportions of patients whose ulcer was completely healed, 2/18 (11%) in standard care and 5/17 (29%) in cadexomer iodine (RR 2.65, 95% CI 0.68 to 10.89). In addition, there was no statistically significant difference in the outcome of 'wound area reduction of at least 50% or improvement in Wagner grade' between the two groups [12/17 (71%) in Iodosorb and 13/18 (72%) in standard care; RR 0.98, 95% CI 0.64 to 1.49]. No adverse events were documented. Six patients withdrew from the study owing to violation of inclusion criteria, hospitalisation, non-adherence to treatment and insufficient data on resource use.

Since there were no significant differences in clinical effectiveness between the two study groups, a cost-minimisation analysis was performed by the same authors using the 1993 exchange rate for the Swedish Kroner (SEK).[122,126] The analysis focused upon resource use in terms of dressing changes, drug prescription, materials consumption and time involved. Costs were estimated for dressing

materials, drugs, staff, transport and others relating to secondary complications. There were a higher (mean) number of dressing changes per week in the standard care group (9.9, range 3.12–13.9) compared with the cadexomer iodine group (4.7, range 3.2–6.9). The authors did not provide sufficient data for the CIs for the difference in the number of dressings changes per week to be calculated. More dressings were performed by nurses and auxiliary nurses, rather than patient or spouse, in the standard care group. The authors reported the time for each dressing change, 13 minutes (range 8–24) for cadexomer iodine, 11 minutes (range 5–23) for standard care, and the mean number of weeks of treatment needed, 10 (range 1–12) in cadexomer iodine, 11 (range 5–12) for standard care. They stated that these were similar between the two groups, although statistical significance was not reported. Mean staff costs were reported as significantly higher in the standard care group (884 SEK, range 315–1492) than the cadexomer iodine group (380 SEK, range 96–570) (authors state $p < 0.001$), but insufficient data were provided to calculate CIs for the difference. Mean weekly transport costs were reported as significantly higher in the standard care group (243 SEK, range 76–341) than the cadexomer iodine group (100 SEK, range 29–156) (authors state $p < 0.001$), but insufficient data were provided to calculate CIs for the difference. As the staff costs and transport costs were both higher in the standard care group, the mean total weekly costs were also higher. Costs of materials and drugs were lower in the standard care group (294 SEK, range 37–981) compared with the cadexomer iodine group (423 SEK, range 166–1113). The authors state that this difference is not statistically significant but insufficient data were provided to allow calculation of the CIs for the difference. Following a synthesis of costs and benefits, the weekly cost per patient healed was higher in the standard care group (12,790 SEK) than the cadexomer iodine group (3070 SEK). The authors state that this difference is not statistically significant but insufficient data were provided to allow calculation of the CIs for the difference. Sensitivity analysis was carried out to test whether the findings were affected by variations in assumptions about travel distance and costs, the number of home-based dressing changes, different staff categories being responsible for care, adherence to regimen and adverse reactions relating to treatment. Reducing the costs of staff travel (from 10 to 5 km) reduced the cost of standard care by 31% and of cadexomer iodine treatment by 20%. Changing the grade of staff changing the dressing so that an auxiliary performed all reduced the cost of standard care by 9% and of cadexomer iodine treatment by 7%.

Assuming that a patient or their carer performed 50% of dressing changes, rather than a paid health professional, reduced the cost of standard care by 40% and of cadexomer iodine treatment by 27%.

Assuming that the dressings were changed as per physician's instructions at all times (e.g. daily) meant that the cost of standard care reduced to 1914 SEK and that of cadexomer iodine to 836 SEK. When the sensitivity analysis included one patient in the cadexomer iodine group who had experienced an adverse event and had been hospitalised, then the cost of cadexomer iodine increased to 1040 SEK and standard care costs were lower, at 903 SEK. Hence the economic analysis is sensitive to inclusion or exclusion of the patient with an adverse event.

Using the matrix of cost-effectiveness,[87,89] and the authors findings that Iodosorb was less costly than standard care, then we find that Iodosorb is preferred, appearing in cell H of the cost-effectiveness matrix in *Box 1*, but this should be interpreted with caution as the costs are sensitive to the inclusion of costs of adverse events, and therefore Iodosorb may be more expensive and no more effective (cell B of the matrix in *Box 1*) than standard care.

Marchina and Renzi (1997)[123]

Marchina and Renzi compared an antiseptic spray (content not described) with a 2% eosin and 0.3% chloroxylenol spray in 40 people, of whom 21 had DFUs, over 15 days.[123] Data were reported for the DFU group. Ulcers were dressed with gauze and changed 2–3 times per day. No other antimicrobial agents, analgesics or anti-inflammatory agents were used during the study. At 15 days, 82% of the people in the eosin/chloroxylenol group were completely healed, compared with 50% in the antiseptic spray group. The actual number of ulcers healed was not given for the two groups and was only available from a graph in the trial report, therefore we cannot calculate the RR of healing or the CIs. This trial was too small to detect clinically important difference in healing rates.

Markevich and colleagues (2000)[105]

Markevich and colleagues reported an RCT of larval therapy versus a hydrogel for DFUs (of

neuropathic origin) in 140 inpatients.[105] Larval therapy uses sterile maggots of the green bottle fly (*Lucilia sericata*) to remove dead tissue within wounds, and during this process the larvae ingest bacteria, which are destroyed in the larval gut, and are reputed to have an antibacterial effect. Hydrogel dressings rehydrate dead tissue within wounds and allow the cells within the wound to remove it. The follow-up period was for up to 10 days (after three applications of larval therapy/hydrogel). Complete healing was reported in 5/70 (7.1%) patients in the larval therapy group and 2/70 (2.9%) in the hydrogel group (RR 2.5, 95% CI 0.58 to 10.9). The authors also report outcomes of 'at least 50% reduction in area' and 'granulation tissue covering at least 50% of the wound', but the clinical relevance of these outcomes is not known. For example, it is not clear if halving ulcer area is a reliable interim outcome measure for complete healing, or if quicker progression to a granulated wound bed necessarily leads to quicker healing.

Rhaiem and colleagues (1998)[124]
Rhaiem and colleagues studied 80 hospitalised patients with cutaneous wounds [of whom 65 (81%) had foot wounds].[124] Participants were randomised into three groups: local wound care plus sugar applied into the wound cavity (changed daily), local wound care plus sugar plus systemic antibiotics, and local wound care plus systemic antibiotics. The method of administration of the antibiotics was not stated (intravenous, intramuscular or oral). All participants received standard care comprising debridement, cleansing and drying.

The authors cited other studies that have used sugar as a topical antimicrobial and gave details on the physiological mechanisms to support their claim. The study period was not clear and details were not given with regard to any treatment received by patients between hospital discharge and follow-up. This three-arm study of topical sugar versus systemic antibiotics versus sugar + antibiotics addresses three comparisons:

- systemic antibiotics versus topical sugar
- sugar versus standard wound dressing (when added to systemic antibiotics)
- systemic antibiotic versus no treatment (when added to topical sugar).

There was no statistically significant difference in the healing rates between systemic antibiotics [16/40 (40%)] and sugar [8/16 (50%)] (RR 1.25, 95% CI 0.64 to 2.23).

There was no statistically significant difference in the healing rates between sugar dressings [11/24 (46%)] and standard dressings [16/40 (40%)] when used in the presence of systemic antibiotics (RR 0.87, 95% CI 0.5 to 1.59).

There was no statistically significant difference in the healing rates between systemic antibiotics [11/24 (46%)] and no antibiotics [8/16 (50%)] when added to a local treatment regimen of sugar dressings (RR 1.09, 95% CI 0.55 to 2.07).

This study is too small to be able to detect as statistically significant, clinically important differences.

The usefulness of further data presented on healing rates was limited, given that it was for all wounds (foot, leg and 'other wounds'). Adverse effects were not assessed. Some economic analysis was presented by the authors, who claimed that the average cost of treating the study patients with sugar could be markedly reduced (when compared with hospitalisation) as the majority of care could be home-based, but there was no concurrent collection of economic data or a formal economic analysis. The authors also reported that there was some difficulty in the application of sugar.

Vandeputte and Gryson (1996)[125]
Vandeputte and Gryson compared a hydrogel dressing with dry gauze dressing irrigated with chlorhexidine in an RCT including 29 people with DFUs (setting not stated) over a 3-month period.[125] Hydrogel dressings are said to provide pressure relieving, moisturising and bacteriostatic properties. Chlorhexidine is an antimicrobial agent. Systemic antibiotics and topical treatments/antiseptics were available to all patients if required. The necessity for amputation (one or more toes) was slightly higher in the chlorhexidine group [5/14 (36%) versus (1/15 (7%), RR for amputation 5.4, 95% CI 0.98 to 32.7], but this difference was not statistically significant. Complete healing data (verified by photographic measure) at the end of treatment showed fewer ulcers healed in the chlorhexidine, group [5/14 (36%)], than the hydrogel group [14/15 (93%)] (RR 2.61, 95% CI 1.45 to 5.76). There was a lower incidence of infection amongst patients in the hydrogel group [1/15 (7%)] than the chlorhexidine group [7/14 (50%)] (RR 7.5, 95% CI 1.47 to 44.1). They also reported a reduced requirement for systemic/local antibiotics/topical treatment [14/14 (100%) in chlorhexidine and 1/15 (7%) in the hydrogel group, RR 0.067, 95% CI 0.01 to 0.31].

Two patients died in the chlorhexidine study group during the trial period compared with none in the hydrogel group. Other adverse events were not reported.

The trial was sufficiently powered on the complete healing outcome and infection incidence outcome to detect clinically important differences as statistically significant, but was underpowered to detect other differences in outcomes as statistically significant.

Summary
The five studies of topical interventions, in which there were eight comparisons, found no robust evidence for a statistically significant difference in clinical outcomes associated with any particular topical antimicrobial. Apelqvist and colleagues[122,126] reported lower treatment costs associated with cadexomer iodine ointment versus standard care dressings, but this was not robust to sensitivity analyses. Vandeputte and Gryson[125] reported more ulcer healing with a hydrogel than with a topical antimicrobial (chlorhexidine on gauze), although it is not clear whether an intention-to-treat analysis was performed, whether any assessments were blinded and how comparable the ulcers were at baseline for duration, area and depth.

Effectiveness of other interventions

One study compared a topical and oral intervention with a standard care regimen.[127]

Description of the study

Dwivedi and colleagues (2000)[127]

This 5-year clinic-based RCT was conducted on 100 people. Dwivedi and colleagues compared a therapy (a decoction of plant extracts) based on Ayurvedic principles, administered as both an oral and a topical treatment against standard care – a combination of systemic antibiotics plus metronidazole, local antiseptics and a peripheral vascular dilator.[127] The oral treatment being evaluated was a water-soluble solid extract of *Rubia cordifolia* (Manjishtha) and of *Withania somnifera* (Ashvagandha), each 500 mg, oral, three times per day. Patients were also required to soak the affected part in a luke-warm water decoction of the plants for 30 minutes daily. The authors justify the potential effectiveness of the Manjishtha plant extract on the basis of its ability to remove microangiopathic and atherosclerotic changes inside the arteries/capillaries surrounding the wound area, thus facilitating blood supply and subsequent removal of microbes. The additional properties of Ashvagandha, they believe, improve the immunological status of patients. Patients with non-healing DFUs of 6–12 months' duration were included. Both study groups received regular surgical intervention, e.g. incision or debridement, as required. Some 30% of patients in the standard care group required surgery, compared with 16% in the active intervention group (Ayurvedic medicine). The authors do not report the exact numbers for each group and therefore the CIs and RR cannot be calculated with certainty. However, if the data given represent an intention-to-treat analysis, then the RR of healing with the standard treatment would be 0.53 (95% CI 0.25 to 1.11). Adverse effects were not reported. This trial was underpowered to detect clinically important outcomes as statistically significant.

Summary
There is no reliable evidence of the impact of this combination of interventions on non-healing DFUs with respect to the need for amputation.

Overall summary

The quality of the trials identified was poor and the sample sizes in the majority of trials were insufficient to identify clinically important differences in effectiveness as statistically significant. There was wide variation in the outcomes reported and the possibility that unfavourable outcomes were not reported whereas equivocal or positive ones were, cannot be excluded, as trials rarely specified primary outcomes measures *a priori*.

Twenty-three trials made 19 unique comparisons between interventions. Three comparisons were replicated: oral ofloxacin versus topical pexiganan in two trials, G-CSF growth factor versus placebo in two trials and G-CSF growth factor versus standard care in two trials, and one trial had three arms, comparing sugar, standard care and antibiotics. None of the trials used a CONSORT checklist for reporting, but some predate its publication. Our criticisms of study quality may reflect poor reporting rather than poor trial design, but without sufficient information the reader cannot determine whether sources of bias and error were minimised or not.

There is no strong evidence for recommending any particular antimicrobial agents for the prevention of amputation, resolution of infection or ulcer healing. Results suggest that growth factor (G-CSF) was less costly than standard care, cadexomer iodine dressings may be less costly

than standard care (daily dressings) and A/S was less costly than A/C. These results are from small, single trials and need replication. Topical pexiganan cream may be as effective as oral antibiotic treatment with ofloxacin.

Decision analytic modelling

This section of the results describes the structure of the decision analytic model constructed to investigate the clinical effectiveness and cost-effectiveness of different diagnostic tests for the identification of infection in patients with a DFU. The first step in the construction of the model was to conduct a review of the literature to identify any models that described the natural history of patients with DFUs, and to identify studies that could inform the transitions within a decision analytic model. We searched for economic models or decision analytic models, i.e. studies in which a mathematical structure had been used to represent the health and/or economic outcomes of patients with a DFU. *Table 2* describes the sources used to identify research. The results of all searches were scrutinised to identify potentially relevant studies.

We report the results of a review of the literature and then describe the general structure of the natural history of one DFU model selected for the investigation of the potential impact on health and economic outcomes of using different diagnostic tests to identify infection in patients with DFUs. Next, we describe the initial assumptions regarding the volume of healthcare resources required for the treatment of patients with DFUs and the way in which the use of diagnostic test would influence and/or modify the natural history, that is, prognosis and treatment of patients with DFUs. The information requirements to inform this new model are then listed. Finally, we discuss the alternatives to using data from research studies as a method of populating the decision analytic model.

Review of previous models describing the natural history of diabetic foot ulcers

The literature review of models describing the 'natural history of individuals with diabetic foot ulcers' [natural history of disease: the temporal course of disease from onset (inception) to resolution] identified five different decision analytic models (decision analytic model: the application of explicit, quantitative methods that quantify prognoses, treatment effects and patient values in order to analyse a decision under conditions of uncertainty) investigating a number of treatment and preventative strategies for diabetic patients at risk of or who have already developed a foot ulcer.[15,121,128–130] Among the five different models identified, there was only one which provided a comprehensive description of the natural history of patients with diabetic foot ulcers;[130] however, for completeness, a brief description of the structure of the identified models is provided below.

Tennvall and Apelqvist (2001)[128]

Tennvall and Apelqvist report the findings of a model that evaluated the cost-effectiveness of two competing alternatives for the prevention of diabetes-related foot ulcers and amputations.[128] The economic evaluation took the form of a cost–utility study in which the health benefits associated with the two alternative preventive strategies were measured in terms of quality-adjusted life-years (QALYs). Mean estimates of costs and health benefits associated with each alternative were derived using a decision analytic Markov model. Transition probabilities for the model were obtained from a survey of 1677 diabetic Swedish patients aged 24 years and over, mean age 66 years. Estimates of the treatment costs were retrieved from a previously published study that reported an analysis of the long-term costs for foot ulcers in diabetic patients within a multidisciplinary setting.[131] Similarly, utility weights associated with the eight health states considered in this model were based on the findings of a previously published study in which the health-related quality of life (HRQoL) of patients with diabetes mellitus and foot ulcers was investigated using the EuroQol questionnaire.[132] The main objective in this analysis was to explore the cost-effectiveness of prevention in four groups of diabetic patients at different risks of developing foot ulcers and/or experiencing amputation. Consequently, the description of the natural history of DFUs was mainly focused in those health states more likely to result in amputation. Although a 'deep foot infection' health state in the presence of an open ulcer was included in the model, no attempt was made to identify foot infections at an earlier stage, the time point at which the contribution of formal diagnostic test may be most valuable.

York Health Economics Consortium (YHEC) (1997)[129]

YHEC conducted a cost-effectiveness analysis of tissue engineered human dermal replacement compared to conventional therapy in the treatment of DFUs in the UK.[129] A model-based economic

evaluation analysis was conducted using a decision analytic Markov model. Health benefits were measured in terms of ulcer-free weeks. Transition probabilities used in the model were derived from the results of an RCT of bioengineered human dermal replacement.[133] Resource use was estimated from the experience at four major UK NHS diabetic centres. The unit costs were retrieved from a variety of sources. Although the structure of this model did distinguish between health states according to varying degrees of infection, the model was not described in sufficient detail to be useful in facilitating the construction of a comprehensive natural history model.

Edmonds and colleagues (1999)[121]
Edmonds and colleagues report on the results of a retrospective cost analysis of rhG-CSF versus placebo in the treatment of hospitalised diabetic patients with infected foot ulcers and extensive foot cellulitis, of whom 39/40 had an ulcer.[121] A decision tree was constructed to estimate mean expected costs for both alternatives. Transition probabilities and total volume of resource use were derived from a randomised double-blind placebo-controlled study.[100] This analysis only considered the cost implications associated with the treatment of diabetic patients with an acute spreading of infection, presumably the patient group for which rhG-CSF is indicated. However, it does not provide information regarding patients with a lesser degree of infection and as such it was not useful for this project.

Eckman and colleagues (1995)[15]
Eckman and colleagues report the findings of a cost-effectiveness analysis of different alternatives for the diagnosis and treatment of patients with type 2 diabetes mellitus, an infected DFU, and suspected osteomyelitis.[15] A Markov state transition model was constructed to estimate mean life expectancy and cost. This model considered three treatment strategies: (1) a short course of antibiotics; (2) empirical treatment of osteomyelitis with a long course of antibiotics; and (3) testing various combinations of roentgenography, technetium-99m bone scanning, white blood cell scanning and magnetic resonance imaging. Life expectancy was adjusted for changes in quality of life. In the base case analysis, quality-adjusted scores were based on expert physicians' judgments. Although this model directly evaluated different diagnosis strategies for infection in patients with DFUs, there were three main factors that prevented us from following this structure in our evaluation. First, a detailed description of the model structure was not provided in the report. Second, the study focused only on patients with a severe degree of infection, who were suspected of suffering from osteomyelitis. Third, the diagnostic test(s) under evaluation is (are) used to detect osteomyelitis rather than soft tissue infection associated with diabetic foot ulcers.

Persson and colleagues (2000)[130]
Persson and colleagues developed a Markov model to evaluate the cost-effectiveness of treating diabetic lower extremity ulcers with recombinant human platelet-derived growth factor (rhPDGF-BB: becaplermin gel, Regranex®) in four European countries: France, Sweden, Switzerland and the UK.[130] Model results have been reported in the literature on a single-country basis and also in an encompassing multi-country analysis. The structure of the model described in this analysis was not only sufficiently detailed and transparent, but importantly, it provided a comprehensive description of the natural history of patients with DFUs. Consequently, it was decided to utilise this model as the basic structure for the analysis. The authors of the UK analysis were contacted and kindly agreed to provide us with an electronic copy of their model.[134]

A model to describe the natural history of diabetic foot ulcers

Model structure

Persson and colleagues' Markov model was adapted and used to describe the natural history of DFUs.[130] This type of model was used as it allows the simulation of disease prognosis incorporating the complications and reoccurrences associated with DFUs over a lifetime. The model describing the natural history of DFUs consisted of nine discrete health states, although in the Persson model there were only six. The states in the adapted model comprised uninfected ulcer, infected ulcer, healed ulcer, gangrene, gangrene history of amputation, healed history of amputation, uninfected history of amputation, infected history of amputation and death. These states represent what appear to be clinically and economically important events in the disease process being modelled. All of the states are mutually exclusive, since one of the requirements of a Markov model is that a patient cannot be in more than one state at a time. By attaching estimates of both resource use and health outcome consequence to the states and transitions throughout the model and then running the model for a specified number of cycles, it is possible to estimate the long-term costs and outcomes associated with the disease and intervention being modelled.[135] Amputation was

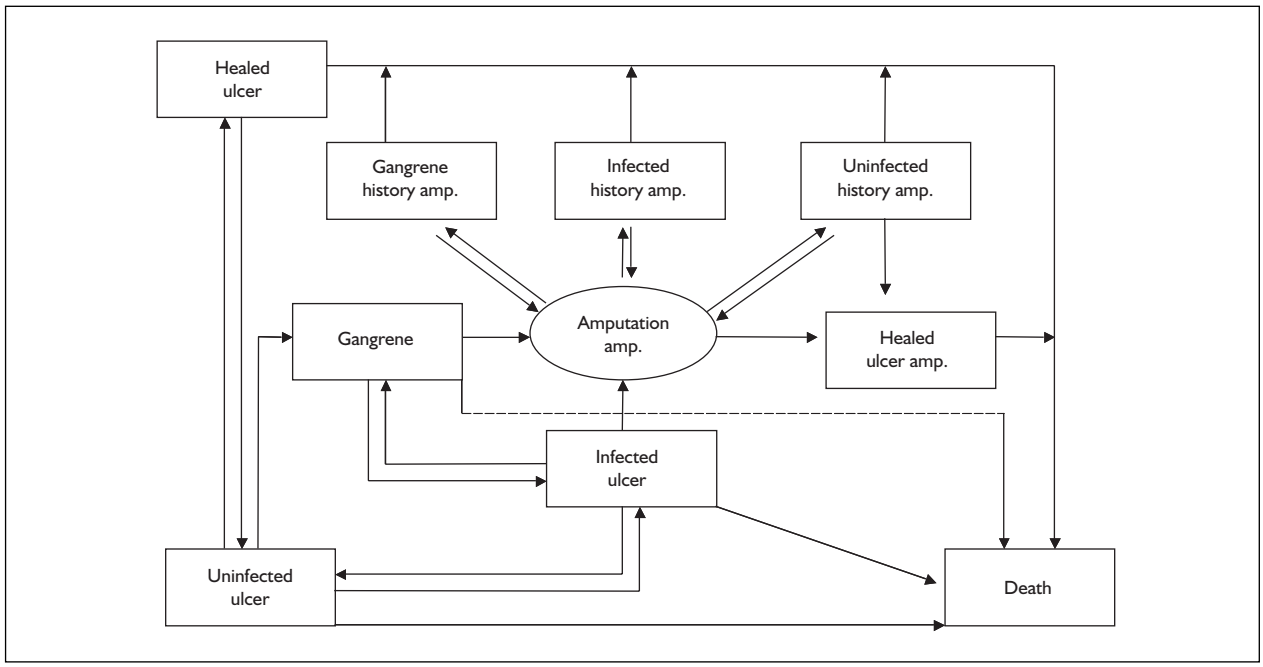


FIGURE 6 *Natural history of diabetic foot ulcers (Markov model)*

considered to be a treatment that aided healing and as such was not considered a health state.

Transition probabilities

Movement between the states is determined by transition probabilities, and takes place after a predetermined length of time known as a cycle. Cycle length should be determined according to the frequency with which patients are likely to change states in real life. In this model, patients were allowed to transit between states at monthly cycles.

In Persson's natural history of the disease model, some transitions between states were disallowed, for example, a person could not develop an ulcer after having an amputation (see *Figure 6*). The Persson model was based on a patient population who were suffering from deep, ischaemia-free, diabetic neuropathic lower extremity ulcers.[130] Consequently, it was necessary for the model structure to be modified to allow transitions that had previously been ruled out, thus allowing the model to reflect the clinical pathways of patients with different underlying causes for DFUs, such as neuropathy and/or ischaemia. These conditions cover the largest proportion of patients with diabetic foot ulcers.

The achievable transitions allow the patient to move from the uninfected state to the healed, infected, gangrene or deceased state; from the infected state a patient can make the transition to the uninfected, gangrene, healed history of amputation, infected history of amputation or deceased state; and from the gangrene health state a patient can make transitions to the infected, gangrene history of amputation, healed history of amputation or deceased state; from the healed history of amputation state a patient can only make the transition to deceased. The deceased health state is an absorbing state from which no transitions can be made. An adaptation of the original model is the transition from uninfected to gangrene. Originally disallowed, this transition was incorporated into our model to allow for a more diverse study population that included ischaemic patients.

The transition probabilities used in Persson's model were derived from a cost of illness study conducted in the USA. The study sample comprised 183 US patients with either type-1 or type-2 diabetes.[136] The transition probabilities were derived directly from the study data (see *Table 11*). Additionally, to ascertain the transitions that rely on information about the rates of successful or unsuccessful amputation, the study data were augmented by Persson and colleagues using estimates based on the literature or expert clinical opinion.[137,138] The transition cycles of the model are monthly and the simulation is run until all patients are healed or deceased.

Model assumptions

Persson and colleagues made a number of model assumptions, which were necessary to facilitate

TABLE 11 *Model transition probabilities*

Transition	Probability	Reference
Uninfected to healed	0.0787	136
Uninfected to infected	0.0473	136
Uninfected to dead	0.004	136
Healed to uninfected	0.0393	136
Healed to dead	0.004	136
Infected to uninfected	0.1397	136
Infected to gangrene	0.0075	136
Infected to healed (amputation)	0.045	131, 137
Infected to infected (amputation)	0.0037	131, 137
Infected to dead	0.0098	136
Gangrene to healed (amputation)	0.3082	131, 137
Gangrene to gangrene (amputation)	0.1818	131, 137
Gangrene to dead	0.0098	136
Healed (amputation) to dead	0.004	136
Uninfected to gangrene[a]		

[a] No information regarding this transition probability was identified in the literature. However, for completeness this transition was allowed in the model since this is a transition patients with arterial insufficiency can make.

completing the natural history model. The assumptions were made both to simplify the modelling process and to supplement the lack of available evidence to inform a different modelling solution. First, it was assumed that after receiving an amputation that resulted in healing, it was not possible for a patient to have a recurrence. Also, it was assumed that amputation did not increase the risk of mortality and that a gangrene ulcer had the same mortality rate as an infected ulcer. Finally, it was assumed that infected ulcers are the cause of approximately 80–85% of all ulcer-related amputations and that gangrene is the cause of the remaining 15–20%.[130]

Elicitation of utility values

It was expected that the main outcome measure of the model would be cost per QALY. Identification of studies reporting utility and HRQoL scores for diabetic patients with and without DFUs was part of the main electronic searches for the project. Two suitable studies were identified.

Sullivan and colleagues (2002)[139]

Sullivan and colleagues elicited patient preferences using both a rating scale and a standard gamble technique.[139] The rating scale technique involves a scale from 0.0 to 1.0 which represent the worst and best conceivable health states, respectively. The individual is then asked to place health state descriptions on the scale. The ratings given to each health state description subsequently represent the individual's rating scale values.

The standard gamble technique involves the individual being given two options and asked to make a choice as to which option they prefer. The options are varied slightly and re-administered to the individual in an attempt to reach the point at which the individual is indifferent between the choices with which they are faced. When this point has been reached, it is possible to ascertain the individual's standard gamble value for the health state selected. The standard gamble technique is considered by many health economists to be the gold standard approach to eliciting cardinal health state values. This is because the technique is grounded in expected utility theory, the dominant economic theory of risk.[140]

The patient population comprised adults with type 1 and type 2 diabetes aged between 18 and 80 years. Patients were excluded if they had any symptoms of diabetic peripheral neuropathy (DPN) such as numbness, tingling or pain in their extremities or any history of lower extremity complication such as a foot ulcer or an amputation. A total of 52 patients were enrolled in the study. Patients were given detailed descriptions of seven health states which fully described the stages of disease severity in DPN. The patients then completed the preference assessment interview for DPN-related health states. The study found that patients' preferences for health states decreased as a function of increasing disease severity in DPN regardless of the methods used to measure preferences. The results of the study are presented in *Table 12*.

TABLE 12 *Health-related quality of life states*

Model health state	Tennvall health states[141]	Sullivan health state[139]
Healed	Primary healed, no amputation	Severe neuropathy
Uninfected	Current foot ulcer, no amputation	Minor ulcer
Infected		Severe ulcer
Gangrene		Severe ulcer
Uninfected (amputation)		Severe ulcer
Infected (amputation)	Maximal major amputation	Major amputation
Healed (amputation)	Maximal minor amputation	Minor amputation
Gangrene (amputation)	Maximal major amputation	Major amputation

When eliciting values for health states, the population chosen can or cannot suffer from the disease in question. Arguments against and in favour of either approach are a subject of debate for many economic experts. For some the preferred method would be to elicit preferences from patients who are currently experiencing the health state; however, others will argue that individuals who are not experiencing such health condition are more likely to make an objective valuation. It is highly likely that Sullivan and colleagues chose to exclude patients suffering from DPN to allow an adequate recruitment sample to the study.

Tennvall and Apelqvist (2000)[141]
Tennvall and Apelqvist (HRQoL) used the EuroQol quality of life questionnaire (EQ-5D), which included a visual analogue scale (VAS).[141] The questionnaire was distributed by postal survey at the end of a 3-year period to type 1 and 2 diabetic patients who had been treated for foot ulcers during the 3-year study period. A total of 440 patients participated in the study and were sent questionnaires. The study had a 70% response rate.

The study protocol defined four mutually exclusive groups dependent on their foot ulcer and amputation status at the time of the questionnaire. The four groups were current foot ulcer with no previous amputation, primary healed with no current amputation, maximal minor amputation and maximal major amputation. The study presents values for both EQ-5D and the VAS; the results of the study are presented in *Table 13*. The study findings show that patients under current foot ulcer treatment value their HRQoL lower than those who have healed primarily without amputation. In addition, quality of life is reduced after major amputations.

Utility values used in the model
The health states which patients were asked to value in these two studies did not directly match those considered in this model. To facilitate their use, the differing health states were matched where possible using both the Wagner scale,[142] which is a widely used classification tool in the clinical field, and the health state descriptions as presented by the individual papers (see *Table 12*). Where necessary, the project team used assumptions and previous experience to ensure the best possible match was achieved (see *Table 13*).

Given that the standard gamble is considered to be the 'gold standard' approach, it was determined that the scores obtained using this technique would be used in the base-case model. Further, the other scores would be used to facilitate sensitivity analysis in an attempt to assess the robustness of the model results obtained.

Healthcare resource use requirements
The perspective adopted for the economic analysis is that of the UK NHS and Personal Social Services and as such only direct costs are included. Resource utilisation for the UK corresponds to that reported by Ghatnekar and colleagues.[143] Unit costs were derived from a number of sources including the BNF, NHS 2000 reference costs and previously published studies.

The unit costing and resource use used in the base-case model are presented in *Tables 14* and *15*.

The prices are expressed in 2000 values. The model applies a discount rate of 6% to costs and 1.5% to benefits according to NICE guidance for economic evaluation analysis.[144]

Based on Ghatnekar and colleagues' assumptions regarding volume of healthcare resources used,

TABLE 13 *Health-related quality of life scores*[a]

Health state	Standard gamble Mean (SE) Range (0.0 –1.0)[139]	Rating scale Mean (SE) Range (0.0–1.0)[139]	EQ-5D Mean Range (–0.594 to 1)[141]	VAS Mean Range (0–100)[141]
Uninfected	0.76 (0.23)	0.57 (0.16)	0.44	52
Healed	0.84 (0.19)	0.70 (0.15)	0.6	63
Infected	0.62 (0.30)	0.41 (0.17)		
Gangrene	0.62 (0.30)[a]			
Uninfected (amputation)	0.62 (0.30)[a]			
Healed (amputation)	0.74 (0.24)	0.45 (0.19)	0.61	64
Infected (amputation)	0.61 (0.29)	0.27 (0.19)	0.31	54
Gangrene (amputation)	0.62 (0.30)[b]			

[a] Higher scores indicate better health status.
[b] Assumption.

the total monthly recurring and non-recurring costs per patient for each health state were estimated to be for the uninfected state £1248.47, for the infected state £1237.44, for the gangrene state £2220.95 and for the healed state £14.01.

Incorporation of diagnostic test in the model structure of the natural history of diabetic foot ulcers

The use of a diagnostic test can facilitate early detection of infection and allow a treatment package to be tailored to meet the requirements of the individual patient. Consequently, the incorporation of a diagnostic test to the model allowed the patients to be split into two groups, those with a positive test result and those with a negative test result, with each group following a different treatment pattern.

The two groups then enter into two different trajectory paths within the model. Those with a positive test result enter their model in the infected state *(Figure 7a)*. Transitions through the model follow the same structure as the natural history model, although the rate at which each transition is made will vary. Those patients who have a negative test result enter their model in the uninfected state and will follow the same structure as the natural history model, (*Figure 7b*). Although, as with the patients who had a positive test, the transition probabilities will vary from those in the natural history model.

Target population

The identification of the target population, that is, those patients with DFU most likely to benefit from the use of diagnostic tests to inform their treatment, was made based on the findings from the systematic reviews conducted within this project and consultation with clinical experts. Applying a diagnostic test for infection to all patients with a DFU irrespective of the condition of their ulcers might be an inefficient use of already scarce UK NHS resources, hence the relevance to identify the groups of patients who are more likely to benefit. Initially, the research team identified clinically infected patients as the target population for diagnostic testing. The literature was then used to characterise this target population fully.

The review of the literature found no consensus on a definition of what it means to be clinically infected. Owing to the lack of clarity surrounding an appropriate definition of 'a clinically infected ulcer', current clinical procedure, the relevance of our target population, and data for the model, it was decided to construct a questionnaire to be administered to what was deemed a relevant audience in an attempt first to derive a definition for clinically infected foot ulcers from clinical experts and to estimate relevant parameters for the decision model using clinical judgement. A questionnaire was designed and personal interviews conducted at the 13th Conference of the European Wound Management Association, Pisa, Italy, 22–24 May 2003. The target audience at the conference was expert wound care researchers and clinicians. Personal interviews were conducted in an attempt to ascertain a consensual definition of 'clinical infection' which could help us to characterise fully the population of interest (see Appendix 7). This in turn would lead to clarification of the relevant economic question.

TABLE 14 *Healthcare resource use requirements associated with the treatment of diabetic foot ulcers (Ghatnekar's assumptions)*[143]

	Quantity	Unit cost (£)
Topical treatment per visit (outpatient)		
• Patients were assumed to require 6 visits per week		
8-Ply gauze swab	1	0.0338
Conforming bandage	0.5	0.435
Nursing cost	1	22.00
Infected patients treated as outpatients		
• 14 days of treatment		
• After 14 days 20% required hospital treatment		
Amoxicillin	1500 mg	0.15
Flucloxacillin	2000 mg	0.498
Infected patients treated as inpatient		
• Treatment continued for 14 days		
I.v. Ceftazidime	4000 mg	39.60
Metronidazole	1500 mg	10.23
Antibiotics – daily treatment (gangrene)		
• 14 days of treatment		
• After 14 days 50% of patients require hospitalisation		
And 50% are treated as outpatients and require metronidazole		
Gangrene treatment as outpatients		
• Treatment continued for 14 days		
Ciproxacillin	1000 mg	2.84
Amoxicillin	1000 mg	0.15
Flucloxacillin	2000 mg	0.498
Metronidazole (50% require)	1200 mg	0.649
Gangrene treatment as inpatients		
• 50% require inpatient treatment for 14 days		
I.v. Ceftazidime	4000 mg	39.60
Metronidazole	1500 mg	10.23
Other outpatient costs (infected and uninfected)		
Podiatrist visit	4 per month	16.00
Diabetologist	1 per month	73.00
Other outpatient costs (gangrene)		
Surgical consultation	1 per year	89.00
Inpatient care		
Length of stay	14 days	
Amputation	Major	7224.00
	Minor	3052.00
Prostheses	1	NA
Orthopaedic appliances		
• A percentage of patients are assumed to require orthopaedic appliances		
Air cast (30%)	1	100.00
Healing shoes (Neoprene) (70%)	1 pair	27.50
Custom shoes (30% of healed)	1 pair	375.00
Orthopaedic stock shoes (70% of healed)	1 pair	100.00

NA, not available.

The results of the interviews revealed that in practice in the UK any patient showing any signs of an infection would receive a first course of antibiotics when they first presented to a clinician. The only patients whose treatment would be informed by diagnostic tests are those who show no signs of infection but whose ulcer is not healing and those in whom a first course of antibiotics was not successful. These two groups of patients then became our new target populations.

Model information requirements

In order to operationalise the model, estimates of all the parameters within it, such as transition probabilities, sensitivity of different diagnostic tests, among others, and the uncertainty

TABLE 15 *Clinical and diagnostic tests assumed to be required by diabetic patients with an open foot ulcer*[a]

Test	Frequency	Unit cost	Uninfected (monthly)	Infected (monthly)	Gangrene (monthly)
Blood glucose	4 times/month	1.10	4.40	4.40	4.40
X-ray	1 time/year	40.0	3.33	3.33	3.33
Full blood count	2 times/year	3.73	0.62	0.62	0.62
U + E	1 time/year	4.00	0.33	0.33	0.33
Blood culture	1 time/year	8.05	0.67	0.67	0.67
Chest X-ray	1 time/year	13.77	1.15	1.15	1.15
$HbA1_c$	1 time/3 months	1.10	0.37	0.37	0.37
Diagnostic tests		**Quantities**	**Unit costs**		
Wound swabs		1	7.9 (5.61–9.33)		
Wound biopsy		1	7.9 (5.61–9.33)		
Wound lavage and analysis of the fluid		1	7.9 (5.61–9.33)		

[a] As testing does not take place in the healed and dead state, no testing costs are incurred for these states.

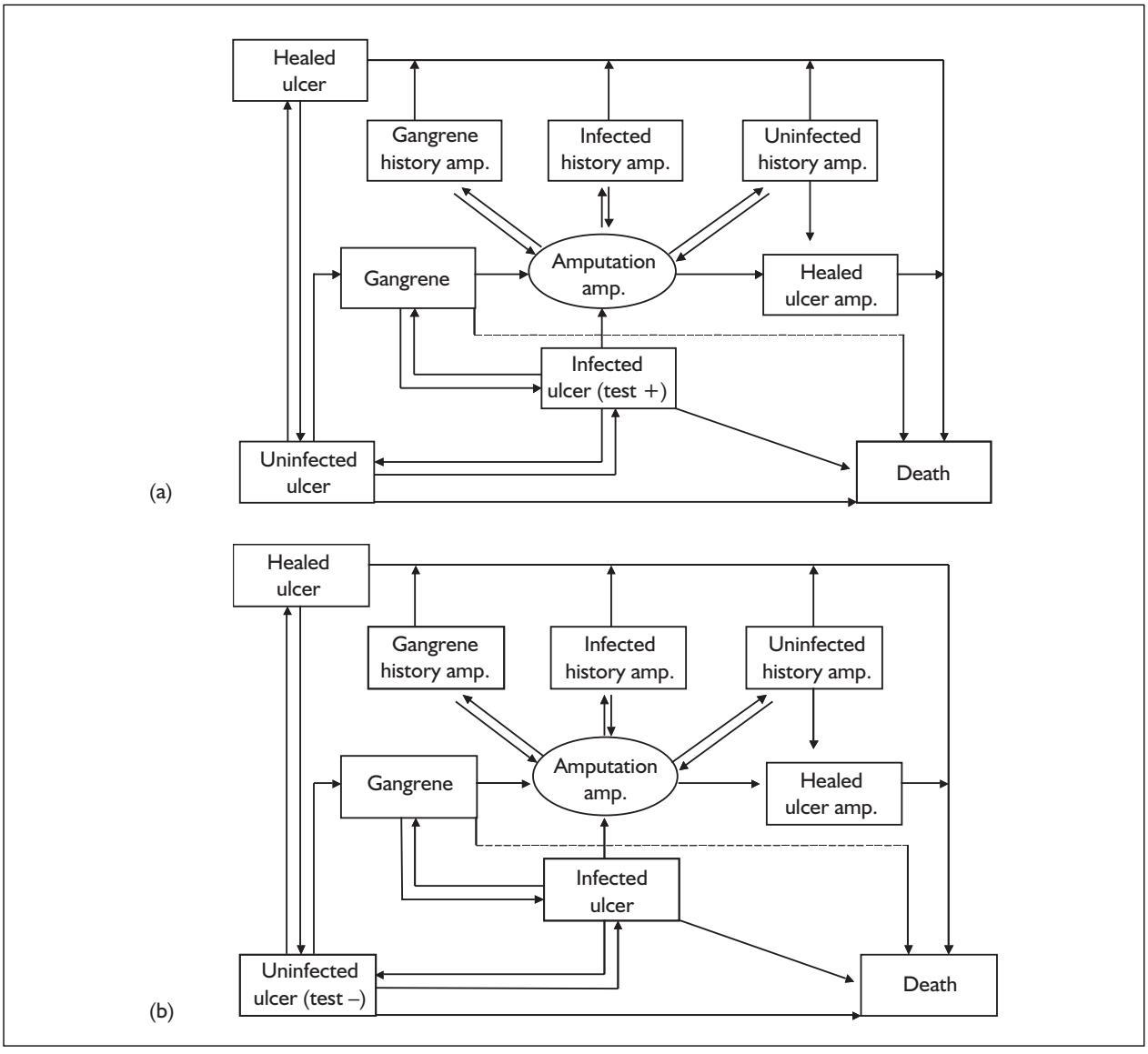


FIGURE 7 *Model structure*

associated with them are required. The model information requirements are described in *Tables 16–19*. It is worth noting that these data should be specific to the two groups of patients with DFUs in which diagnostic tests are routinely used in the UK, namely:

- Patients with DFUs who do not show any clinical symptoms of infection but whose ulcer is not healing.
- Patients with diabetic foot ulcers in whom a first course of antibiotics was not successful.

TABLE 16 *Diagnostic information requirements to run model*

Diagnostic test	Information required
Wound swabs	Sensitivity and specificity
Wound biopsy	Sensitivity and specificity
Wound lavage and analysis of the fluid	Sensitivity and specificity

TABLE 17 *Effectiveness information requirements to run model*

Impact on treatment	Information required
Wound swabs	Expected changes in antibiotic treatment effectiveness (i.e. changes in proportion of patients whose infection resolves) due to prompt detection of infection using this test
Wound biopsy	Expected changes in antibiotic treatment effectiveness due to prompt detection of infection using this test
Wound lavage and analysis of the fluid	Expected changes in antibiotic treatment effectiveness due to prompt detection of infection using this test

TABLE 18 *Outcome information requirements to run model*

Transition probabilities	Information required
Uninfected to healed	Proportion of patients with an uninfected ulcer who heal
Uninfected to infected	Proportion of patients with an uninfected ulcer who are later diagnosed as infected
Uninfected to dead	Proportion of patients with an uninfected ulcer who die
Healed to uninfected	Proportion of healed patients who have an ulcer recurrence
Healed to dead	Proportion of healed patients who die
Infected to uninfected	Proportion of people diagnosed as infected whose infection resolves after a first course of antibiotics
Infected to gangrene	Proportion of people with an infected ulcer who are later diagnosed as having gangrene
Infected to healed (amputation)	Proportion of infected people who undergo amputation Proportion of people with an amputation who heal
Infected to infected (amputation)	Proportion of infected people who undergo amputation Proportion of people with an amputation who are later diagnosed as infected without having healed
Infected to dead	Proportion of infected people who die
Gangrene to healed (amputation)	Proportion of people with an infected ulcer who are later diagnosed as having gangrene Proportion of people with gangrene who undergo amputation Proportion of people with gangrene who heal after amputation
Gangrene to gangrene (amputation)	Proportion of people with an infected ulcer who are later diagnosed as having gangrene Proportion of people with gangrene who undergo amputation Proportion of people with gangrene whose gangrene reoccurs after amputation
Gangrene to dead	Proportion of people with gangrene who die
Healed (amputation) to dead	Proportion of people undergoing amputation who heal Proportion of healed people after amputation who die
Uninfected to gangrene	Proportion of uninfected people who are later diagnosed with gangrene without a prior diagnosis of infection

TABLE 19 *Treatment information requirements to run model*

(a) Topical treatment per visit		
Current assumptions in the model regarding topical treatment	*Does this assumption apply to target groups in UK?*	*Quantity*
6 visits per week		
8-Ply gauze swab		
Conforming bandage		
Nursing time		
(b) Treatment of infection (outpatients)		
Current assumptions in the model regarding outpatients' treatment of infection	*Does this assumption apply to target groups in UK?*	*Daily dosage*
Treatment was to be continued for 14 days. After 14 days.		
20% of these patients required hospital treatment		
Amoxicillin		
Flucloxacillin		
(c) Treatment of infection (inpatients)		
Current assumptions in the model regarding inpatients' treatment of infection	*Does this assumption apply to target groups in UK?*	*Daily dosage*
Treatment was assumed to continue for 14 days		
I.v. Ceftazidime		
Metronidazole		
(d) Treatment of gangrene (outpatients)		
Current assumptions in the model regarding outpatients' treatment of gangrene	*Does this assumption apply to target groups in UK?*	*Daily dosage*
Treatment continued for 14 days. After 14 days		
50% of these patients will require hospitalisation and 50% will be treated as outpatients and require metronidazole		
Ciproxacillin		
Amoxicillin		
Flucloxacillin		
Metronidazole		
(e) Treatment of gangrene (inpatients)		
Current assumptions in the model regarding inpatients' treatment of gangrene	*Does this assumption apply to target groups in UK?*	*Daily dosage*
50% require inpatient treatment for 14 days		
I.v. Ceftazidime		
Metronidazole		
(f) Other outpatients' costs (apply to infected and uninfected patients)		
Current assumptions in the model regarding other outpatients' services	*Does this assumption apply to target groups in UK?*	*Quantity*
Podiatrist visit		
Diabetologist		
(g) Other outpatient costs (apply to patients with gangrene)		
Current assumptions in the model regarding other services for patients with gangrene	*Does this assumption apply to target groups in UK?*	*Quantity*
Surgical consultation		
(h) Inpatient care		
Current assumptions in the model regarding other services for inpatients	*Does this assumption apply to target groups in UK?*	*Quantity*
Length of stay		
Major amputation		
Minor amputation		
Prostheses		

continued

TABLE 19 *Treatment information requirements to run model (cont'd)*

(i) Orthopaedic appliances		
Current assumptions in the model regarding orthopaedic appliances	*Does this assumption apply to target groups in UK?*	*Quantity*
Percentage of patients who are assumed to require orthopaedic appliances Air cast (30%) Healing shoes (Neoprene) (70%) Custom shoes (30% of healed) Orthopaedic stock shoes (70% of healed)		

According to the results obtained from the systematic review of diagnostic studies, there is a paucity of research regarding the use and contribution of diagnostic tests in the management of patients with DFUs. The review found only three diagnostic studies that were eligible for inclusion and none of them provided information about the sensitivity and specificity of the diagnostic tests for the two target population groups. Equally, the studies reporting on the clinical effectiveness of different antibiotic treatments for infection do not specifically refer to the effectiveness of such treatments for either of the target populations; rather, they refer to a range of patients with an infected foot ulcer/leg. Consequently, the decision analytic model described above could not be informed for the populations of interest. In order to populate the model, the data requirements outlined in *Tables 16–19* would be required. The model could be adapted to suit any patient population that matched the natural history outlined previously and for whom the data could be obtained. At this time no data for our target populations were available. As a result, no estimates of health benefits or costs associated with the use of diagnostic test of infection in the relevant patients with diabetic foot ulcers could be made.

Alternative options to populate the decision analytic model

Given the lack of evidence identified in the review of the literature to populate the decision analytic model described above for the two populations of interest, it was necessary to pursue other avenues that may facilitate the data requirements. Hence the research team decided to consult with clinical experts to explore the possibility of populating the model using clinical judgments.

Aims

An interview schedule was designed with the aim of guiding semi-structured interviews with expert clinicians. The interviews sought to identify a definition of clinical diagnosis of an infected foot ulcer and the clinical symptoms associated with it. Clinicians were then presented a number of alternative courses of action to assess/treat individuals with a DFU who had been clinically diagnosed as having an infected ulcer, and those with a non-healing but apparently uninfected ulcer. This included asking about the type of microbiological sample taken and its role in determining therapy. Finally, interviewees were asked to give their views about a definition of clinical diagnosis of infection in foot ulcers that had been identified in the literature.

Sample

One interviewer approached six international experts working with DFUs who were attending a conference on wound management. They comprised two podiatrists, one diabetologist, one vascular surgeon, one nurse specialist and one physician with an interest in chronic wounds. Responses were recorded on an interview schedule rather than being recorded electronically. Replies were tabulated to identify agreement and disagreement between respondents.

Results

The responses are reported in Appendix 7.

Definition of infection. Four experts reported that swelling was indicative of infection (the other two cited cellulitis), four used pain as a potential marker of infection and four reported discharge or exudate as being important. The primacy of the clinical diagnosis of infection, as opposed to using bacteriology to diagnose infection, is highlighted by the statement by respondent C: "We don't use swabs to diagnose infection, the clinical impression is the diagnosis, swabs simply confirm the organism". Other diagnostic clues for infection included redness or erythema (three reports), smell (three reports), cellulitis (two reports), heat (one report), induration (one report), and undermining (one report).

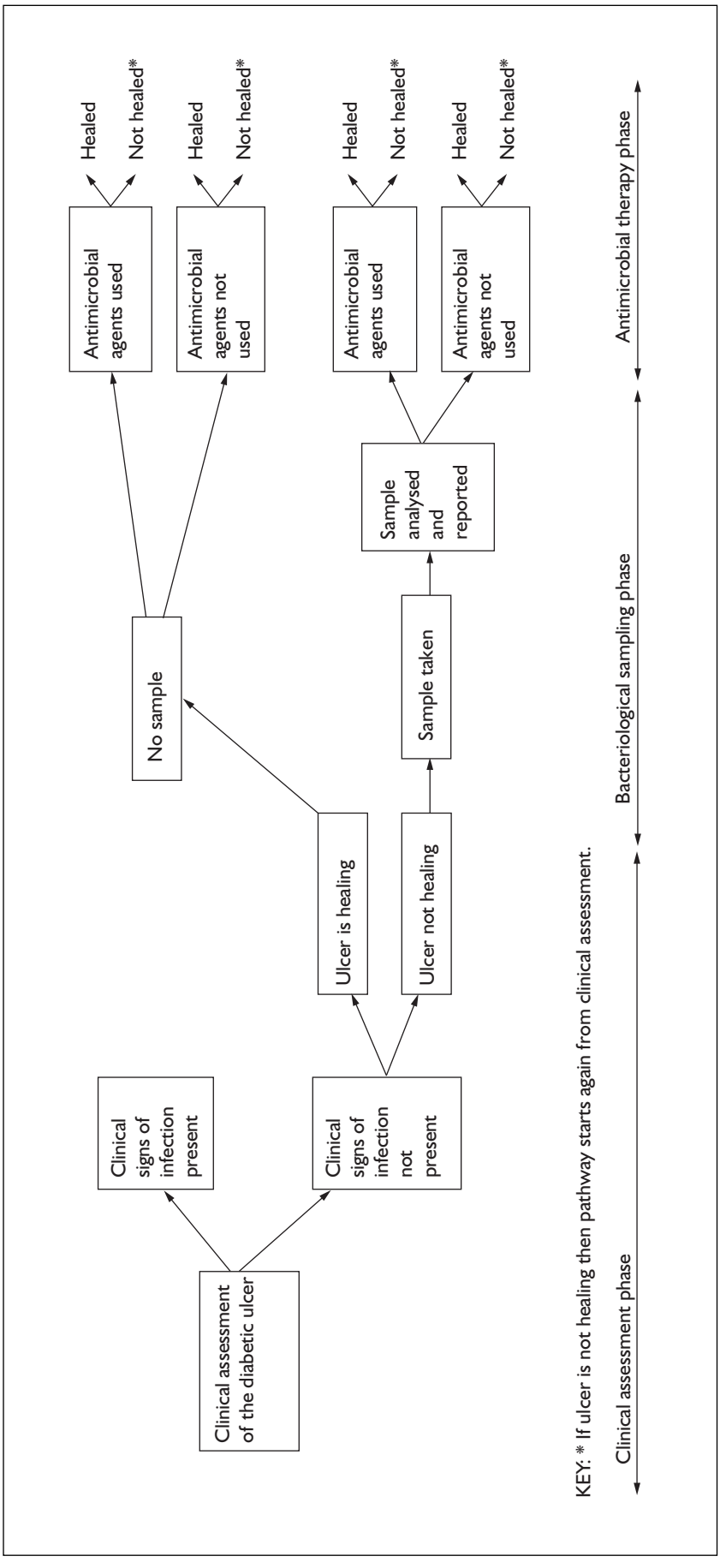


FIGURE 8 *Revised clinical pathway representing current treatment of potentially infected diabetic foot ulcers*

Empirical or bacteriology-guided therapy after diagnosis of infection. When asked whether a course of antibiotics would be commenced following a clinical diagnosis of infection (and before a swab result is available), three experts stated "all of them", one stated "virtually all of them", one stated "the majority" and one "5–7 out of 10". One reason given for delaying antibiotic therapy was the potential for osteomyelitis – it was stated by a podiatrist working in a tertiary referral centre that therapy would await a bone biopsy if osteomyelitis was suspected. Another factor affecting the decision to prescribe empirically or to await results was the day of the week on which the patient was seen – as a patient seen in the early part of the week could be seen again in 24/48 hours to check on progress, whereas someone seen on a Friday could not be reassessed easily, and therefore were more likely to be given antibiotics.

Sources of information on wound bacteriology. Swabs were the most common type of sample taken for analysis (4/6 respondents) with a deep tissue biopsy taken at centre where a bone infection team was available and curettage of neuropathic ulcers at one centre. The role of swabbing was summarised by one respondent who stated that they treat the symptoms, not the swab result (respondent A). Practices following uninformative swabs were variable.

Managing uninfected ulcers For apparently uninfected ulcers, the period of time over which an assessment of 'non-healing' was made ranged from 3 to 8 weeks, although one expert stated that they used the percentage reduction in area by week 4 as a guide.

Caputo's definition of clinical infection[25] All experts agreed with Caputo's definition of infection in diabetic foot ulceration,[25] "erythema, induration and discharge", but one pointed out that the lack of erythema in a neuropathic ulcer may reflect pathology rather than prove the absence of infection. This expert also said that the characteristics of the discharge were important – changes in type/amount of discharge were important as waiting for pus were leaving it "too late". Only one expert stated that the presence of two of the three signs was sufficient, and it is not clear whether the remaining experts required the presence of all three signs for most ulcers.

Other findings from the interviews. The three medical doctors described different empirical regimens for first-line treatment, with two of the three mentioning metronidazole and two mentioning clindamycin.

Summary

The interviewees lacked agreement overall on the diagnostic criteria for clinical infection, the prevalence of infection, the best course of action regarding treatment, length of treatment before an alternative would be tried and the use of diagnostic testing.

Discussion

The variations in clinical practice regarding the type of bacteriological sample taken and use of antimicrobial therapy from the questionnaire's responses raised concerns regarding the appropriateness of using clinicians' estimates to inform the decision analytic model. The variations presented in the clinical estimates were so widely dispersed that it was not possible to obtain a central estimate and use sensitivity analysis over plausible ranges to address the uncertainty in our chosen estimate.

It was decided that the degree of variation reflected in the data suggested that it would not be possible to reach consensus about any of the parameters of interest based on the information from the interviews with the clinicians. At this point, it was decided that the decision analytic model could not be populated.

After considering the response of the interviewees, and looking at the literature available, we were able to revise the clinical pathway initial proposed (*Figure 1*) to reflect the actual pathways that clinicians took. This is summarised in *Figure 8*. In brief, it indicates that antimicrobial analysis for determining the choice of antibiotics to be used for an episode of infection is reserved for patients in whom there are no frank signs or symptoms of infection, but whose ulcer is non-healing. For people with an ulcer infection, a sample may be taken but, as antibiotic therapy is commenced immediately, then the choice of antibiotics is not informed by the results. The results from bacteriological analyses were consulted, according to our interviewees, only if the infection was not resolving or the ulcer was not healing.

Chapter 5
Discussion

Diagnostic studies

Limitations of the research

What is the diagnostic performance of clinical examination in the identification of infection in DFU?

One study was identified that addressed the above research question.[90] The overall sample size was small (n = 36), which meant that some sensitivity, specificity and predictive values were estimated at 100% (likely to be inflated) and therefore that a correction factor of 0.5 was required to calculate some LRs. The derived estimates are likely to have wide CIs, indicating a large degree of uncertainty around the central estimates. The use of a larger sample size would have increased the precision of the estimates.

The sample was heterogeneous with respect to wound type. It is possible that different wound types present differently with respect to different clinical signs and symptoms of infection and that the usefulness of individual signs and symptoms may vary according to wound aetiology. This was reflected in the slightly different profile of sensitivity values seen in venous leg ulcers when compared with the overall sample. Of particular interest is the higher sensitivity for purulent exudate as compared with the overall sample of wounds of mixed aetiologies (67% versus 18%). However, it may be argued that a sensitivity of 67% is still not high enough to be clinically useful, and it would be necessary to consider the clinical and economic consequences of failing to identify one-third of wound infections. Another potential reason for the difference between estimated outcomes across different wound types is random error (chance). Since there were only two patients with DFUs and seven patients with venous leg ulcers, it is difficult to infer from the findings of this small study in a way that is useful to the research questions posed for this project. It is likely that all patients with a chronic wound are likely to be subject to clinical examination of the lesion in clinical practice. However, owing to the strict inclusion criteria in terms of the baseline haematological status of patients in three out of the four study centres, this study is likely to have excluded some patients for whom the index test would be relevant. It is difficult, therefore, to generalise the results of this study to a population seen in clinical practice. Another consideration is that this study estimated diagnostic outcomes for a range of individual clinical signs or symptoms. It may be the case that, in reality, clinicians tend to define infection based on clusters of signs and symptoms rather than relying on any one individually, as described by the expert respondents in Appendix 7.

The assessment of inter-rater reliability of the individual checklist items resulted in κ statistics ranging from 0.53 to 1.00. The authors provided more detail about this assessment in a separate paper.[145] The following can be deduced with the assistance of guidelines for interpreting κ statistics:[146,147] very good agreement (κ = 0.81–1.00) was attained for the symptom of increasing pain, and signs of oedema, delayed healing and wound breakdown; there was good agreement (κ = 0.61–0.80) for erythema, purulent exudate, serous exudate, discoloration and friable granulation; moderate agreement (κ = 0.41–0.60) for heat and foul odour; and no agreement better than chance was found for pocketing of the wound base. In terms of percentage agreement, the study authors made use of recommendations suggesting that an agreement of at least 70% is necessary, at least 80% is adequate and at least 90% is good.[145,148,149] Four of the checklist items had agreement values <70%: heat (occurrence agreement 44%); discoloration (non-occurrence agreement 65%); foul odour (occurrence agreement 50%); and pocketing of the wound base (occurrence agreement 0%). All except pocketing of the wound base, which did not occur in the sample, had favourable alternative agreement values in terms of total percentage agreement, occurrence percentage agreement, non-occurrence percentage agreement and/or κ statistics.[145]

Two clinical indicators (increasing pain and wound breakdown) may be useful individually for identifying infection in chronic wounds, and both showed good inter-rater reliability. However, these findings should be viewed with caution owing to the small size of the study and the heterogeneity of the study group with regard to wound type.

When interpreting outcomes from diagnostic evaluations, it is important to recognise possible sources of bias that may impact on the derived estimates. It was unclear from the paper whether results for each patient for the index test were interpreted without knowledge of the associated result of the reference test, and vice versa. If interpretation was not blind, bias could arise as a result of non-independent assessment of index and reference tests, which is thought usually to result in overestimation of the accuracy of the index test (test review bias).[150] The longer time lag between tests for one of the study sites could have meant that some wounds changed their infection status during the interim period, leading to disease progression bias.

What is the diagnostic performance of specimen acquisition techniques in the identification of infection in DFU?

Findings suggested a limited usefulness for the wound swab in detecting infection in chronic wounds.[91] However, it should be noted that there are several limitations to this study. The overall group size is small and it is heterogeneous with regard to wound type. It is possible that the test could perform differently in different wound types, therefore the estimates reported for the overall sample should be interpreted with caution. It is not clear whether participants had to have wound infection suspected from clinical signs and symptoms in order to be recruited. If not, then the usefulness of taking a swab for all wounds may be questionable, and may not reflect procedures in clinical practice. However, patients had to have wounds present for at least 6 months, and it may be that the study authors considered that delayed healing indicated the presence of wound infection. It is possible that the inflammatory response, and therefore the usual presentation of clinical signs and symptoms of wound infection, may be reduced in people with DFUs, owing to reduced skin vasodilation and/or neuropathy.[24,60] Some sources suggest that the presence of bacteria in wounds may delay healing.[151] However, the currently available evidence on the link between presence of pathogens and wound healing is both sparse and inconsistent.[48,151]

The estimates of diagnostic accuracy gleaned from this study may have been influenced by test review bias.

There was difficulty in identifying a universally accepted reference standard in this field of research. This problem has been observed in other clinical areas and it has been asserted that 'gold standards providing full certainty are rare'.[152] Tissue biopsy was employed as the reference standard for the two studies described above.[90,91] Other sources also suggest that tissue biopsy is a reliable reference standard.[153,154] Given that the difficulty lies in deriving a standard as close as possible to the theoretical reference standard,[152] it seems likely that researchers will continue to regard tissue biopsy as the optimum reference standard for evaluations of diagnostic accuracy. In studies where a reference standard has not been defined and justified, the evaluation should be regarded as assessing the agreement between diagnostic tests as opposed to accuracy. The National Coordinating Centre for Research Methodology (NCCRM) has recently proposed a methodological research project to review methods in diagnostic evaluations when there is no reference standard, which may eventually provide guidance for conducting systematic reviews of this type.[155]

What is the diagnostic performance of different laboratory analysis techniques in the identification of infection in DFU?

Findings, again from a single study, suggest that semi-quantitative analysis may be a useful alternative to quantitative analysis, particularly for settings where the equipment and materials necessary for the latter are not available.[92] The study group was heterogeneous in terms of wound type, and the impact of the use of different techniques of laboratory analysis of swabs in DFUs is unclear. It is not known whether analysis results vary across samples from different wound types when bacterial loads are similar. Owing to the apparent dearth of research in this important area, it is difficult to say whether the use of a quantitative analysis of wound swab is an acceptable reference standard. Test review bias and disease progression bias may have had an impact on the derived estimates, therefore the findings from this study should be viewed with caution, particularly when inferring to a particular wound type.

Reporting issues

In recent years, several initiatives have been developed to help improve the standard of reporting of biomedical research. Initially the Consolidated Standards of Reporting Trials (CONSORT) statement was issued with the aim of improving the reporting of randomised controlled trials.[156] Later, the Quality of Reporting of Meta-Analyses (QUOROM) statement was introduced, a similar tool to the assist reporting of systematic reviews and meta-analyses.[157] More recently, the

Standards for Reporting of Diagnostic Accuracy (STARD) initiative has been described to improve the quality of reporting of studies of diagnostic accuracy and therefore help readers to judge the internal and external validity of an evaluation.[158] The STARD initiative includes the use of a checklist developed by a project steering committee who used literature searches and a consensus procedure to develop the range of constituent items. The checklist covers the following: ease of identification of the article as a study of diagnostic accuracy; description of research questions; methods used for participant selection, test execution and statistical analysis; results in terms of participant characteristics, time interval between tests, distribution of disease severity, diagnostic outcomes and adverse effects; and discussion of the clinical applicability of study findings. With respect to the three studies included in this review, the following were the most important problems with regard to quality of reporting. None of the studies reported whether results of the index test were interpreted without knowledge of the results of the reference test, and vice versa. Only one reported test reliability and described the number, training and expertise of the people performing and interpreting the index test, but no description for the reference test,[90,145] and only one considered the possible impact of adverse effects of the tests in terms of the clinical consequences of false negative and false positive results.[92] Two studies did not state the methods used for selecting participants.[90,92] None of the studies stated whether treatment was delivered to the wound between administration of tests, and in one study the time interval between tests was not stated.[92] In two studies, no information was provided about when the study was done or recruitment dates.[90,91] Although there are clearly some improvements that could have been made to the reporting of all three studies, it is important to acknowledge that all three studies fulfilled many of the items on the 25-item STARD checklist.[158]

Other systematic reviews

No existing systematic reviews addressing the three diagnostic research questions were identified from this project. As far as we can ascertain, this project is the first attempt at combining data from studies of clinical examination and microbiological sampling in DFUs. Two systematic reviews were identified in a related area, not within the scope of this project, the diagnosis of osteomyelitis.[159,160] The earlier review evaluated the diagnostic accuracy of technetium bone scanning for detecting lower extremity osteomyelitis in patients with diabetes, neuropathy or vasculopathy.[159] The more recent review assessed the diagnostic performance of a variety of methods (including imaging techniques, probe to bone and bone biopsy) to identify osteomyelitis in patients with a DFU.[160]

Novel techniques

No evaluations meeting the inclusion criteria were identified for the two novel techniques of wound infection detection, the electronic nose/tongue and PCR. Should these techniques eventually prove to be of value for management of infection in DFUs, they could potentially modify clinicians' decision-making processes, owing to reducing the waiting time for test results.

Recommendations from clinical guidelines on DFUs

A review of clinical guidelines on management of diabetic foot disease shows varying recommendations to inform clinicians about the best ways of identifying infection in DFUs. Some sources recommend the use of clinical examination only, and suggest that cultures are of limited value.[76,78] Other documents suggest that there are problems with clinical examination owing to the absence of many of the classical signs and symptoms of systematic or local infection in diabetic patients.[79] However, swabs should only be used following debridement or curettage of the ulcer bed.[77,79] One recommendation is to commence antibiotic therapy according to clinical signs and symptoms, then modify treatment according to culture results.[161]

The uncertainty reflected by these varying recommendations perhaps reflects the paucity of relevant data, and supports our finding of three eligible studies representing the true extent of the available evidence. Several other relevant clinical guidelines do not contain any information about diagnosis of infection in DFU, which again may correspond to the dearth of research evidence.[162–164]

Adverse effects of diagnostic tests

As identified above with reference to the STARD checklist,[158] only one of the included studies reported on possible adverse effects of the tests in terms of the impact of false negative and false positive results.[92] None of the studies investigated the possible psychological effects of false negative and false positive results (e.g. anxiety) or the impact of pain or discomfort associated with undergoing the tests. Even in the case of clinical assessment of the wound, the patient may be required to assume an uncomfortable position

while the examination takes place. In addition, the acquisition of microbiological samples using tissue biopsy or swab may be painful. Some swabbing techniques require that sufficient pressure is applied to the wound in order to express tissue fluid.[91,92]

A further related concern is whether the wound flora may be altered through the use of different acquisition techniques, such as applying pressure to the wound surface using a swab. It is possible that transient and resident bacterial populations could be differentially sampled using gentle or aggressive swabbing techniques. As far as we could ascertain, this aspect of microbiological sampling has not been evaluated.

Effectiveness studies

Limitations of the research

What impact does microbiological analysis have on therapy?

We did not find any studies evaluating the impact of microbiological analysis on the treatment of infection, pain, exudate, healing, HRQoL or the development of complications. It is possible that in industrialised countries the availability of microbiological testing means that this is routinely done, and the opportunity to conduct a trial may be minimal. In interviews with experts to inform the review (Appendix 7), it was stated that a culture and sensitivity result from a swab or biopsy would be necessary to adjust therapy if the empirically chosen therapy was inappropriate or if the infection failed to resolve. If there is no clinical improvement over a period of a few days, then the swab or biopsy results are consulted to guide the choice of antibiotic. It is not clear how useful the results from a microbiological sample are at this point. As the sample has been drawn from the wound prior to the commencement of antibiotic therapy, the wound flora may have changed. However, without rapid microbiological analysis techniques the initial swab may be the only source of information on the cause of infection, even if it is imperfect.

What are the effects of treatments on clinical effectiveness and cost-effectiveness?

Our second effectiveness question addressed the clinical and cost-effectiveness of techniques for treating infection in DFUs. Outcomes of interest were infection resolution, amputation, healing and the transfer of drug-resistant organisms to staff and other patients. Overall, the strength of the evidence to guide the selection of antimicrobial agents for the treatment of diabetic foot ulcers is poor. This is due to the poor quality of many of the trials and the lack of replication of most comparisons.

Population

While the review aimed to summarise the effect of interventions for treating infection, it became apparent that studies reported the ulcer characteristics in a number of ways. Some described infections associated with foot ulcers as ulcer infection, some as soft tissue infection and others as cellulitis. A number of trials included mixed populations, either people with diabetes and ulcers or soft tissue infection but no ulceration, or people with infected wounds, some of whom had diabetes and foot ulcers. We included trials in which data for infected DFUs were available separately, or where at least 80% of a population of people with infected wounds had foot ulcers and diabetes. A few studies evaluated the impact of antimicrobial agents in the management of apparently uninfected DFUs and these were also included as the clinical diagnosis of 'infected/uninfected' may not be straightforward in people with diabetes owing to suppression of the normal immunological response to infection.[165] Some authors believe that a non-healing wound, even if apparently uninfected, may be delayed in healing due to a 'critical colonisation' of the wound bed by a high bacterial load.[166] We therefore decided to include all trials where an antimicrobial intervention was used, as this would reduce any chance of excluding studies in people with delayed wound healing due to bacterial load.

Defining antimicrobial agents was straightforward for antibiotics, but not for other agents which act by direct ingestion of bacteria (larvae), or reducing osmotic potential for bacterial proliferation (sugar), as a number of different agents potentially redress the host–bacterial balance.[167] We decided to include an agent if it was a recognised antimicrobial (antibiotics and antiseptics, for example) or if the authors of the study stated what antimicrobial action the agent possessed. Agents were included in the review regardless of their mode of administration or their current licensing status. With this definition in use we also included a growth factor which increases neutrophil activity, and which is used in infected ulcers alongside systemic antibiotics.

Comparisons made

The comparisons in the trials tended to be of two active interventions. Notable exceptions were the trial comparing oral antibiotics with a placebo

tablet in 44 people with 'uncomplicated' neuropathic foot ulcers (ulcer grade up to 2A),[74] and the four growth factors trials, in which placebo or standard care alone were the comparators.[100,118–120] For people with a clinical diagnosis of established severe wound/foot infection, it is unlikely that a placebo or standard care controlled trial could be performed as clinicians are convinced of the need to institute immediate antibiotic therapy (see Appendix 7) and delay, for example to culture the causative organisms, or a placebo treatment could threaten the limb. It may be more feasible to conduct a trial comparing antimicrobial agents against placebo/standard care alone in people without a severe infection. This would help inform whether there is a net benefit associated with antibiotic treatment in this group. Such studies, however, rely upon clinicians having access to reliable technologies to distinguish between people with severe or non-severe infections. Interviews with clinicians indicated that decisions to treat empirically or adopt a watchful waiting approach also depended on factors such as their confidence in the patient returning if the ulcer deteriorated, and the proximity to the weekend, when immediate access to the foot clinic is not possible (Appendix 7).

Study quality

We assessed the quality of each trial and presented the Jadad scores for each characteristic separately as simple addition of the scores may be misleading. Overall – the quality was poor – median score for double-blinding was 0 (i.e. trial was not described as double-blind); median score for randomisation was 1 (i.e. trial was simply described as randomised with no details about methods used to achieve randomisation); median score for withdrawals was 1 (i.e. number of withdrawals was reported by groups and reason). Allocation concealment was scored as adequate, unclear or inadequate and the mode was 'unclear'. Two trials described inadequate methods of allocation.[106,122] Two trials described adequate methods of concealing the allocation from the person randomising the participant into the trial.[100,101] Two trials allowed patients to select their own treatment.[110–112]

From the information available, the trial that scored the highest in terms of quality was an evaluation of subcutaneous growth factors,[100] as it described adequate randomisation procedures, allocation concealment, appropriate methods for double-blinding, and reported withdrawals by group and reason.

One study of systemic antibiotics, by Peterson and colleagues,[101] described allocation concealment, appropriate randomisation, described themselves as double-blinded (but did not report how this was achieved), and reported withdrawals by group and reason.

These two studies reported attempts to minimise bias but were too small to allow robust conclusions to be drawn, hence we did not give them additional weight in the narrative review.

Statistical power

Most trials (20/23) did not report a calculation, *a priori*, of the sample size required to be able to detect clinically important difference in outcomes as statistically significant. This means that they had a very high risk of concluding that there was no difference in the effectiveness of the comparator regimens when in reality there was insufficient power to be able to determine whether there was a difference or not (a Type II error). For example, Chantelau and colleagues concluded that there was no benefit to the addition of antibiotics for uncomplicated neuropathic ulcers, but the trial was too small ($n = 44$) to allow one to exclude a clinically important benefit.[74]

Baseline comparability

A large, well-organised RCT with adequate randomisation should distribute people with poor prognosis for healing/resolution of infection equally between the treatment groups. It is desirable, however, to present the characteristics of the people in the trial both to allow readers to assess the similarity of the trial participants to their patient population and to provide these data by treatment groups to see if there were important imbalances in baseline risk at the outset. In a modest-sized trial, this can happen purely by chance, and visual inspection of the results allows one to see if there are imbalances. In addition, it can point one to problems with the randomisation procedure, for example if the people with more severe disease tended to be allocated to one group, then one might investigate whether the randomisation schedule was subverted by clinicians trying to ensure that people with severe disease received the (in their opinion) 'better' intervention. Margolis and colleagues undertook an analysis of the risk factor for healing diabetic neuropathic ulcers in 20 weeks and found that the risk factors for non-healing were increased duration of ulceration, increased area of ulceration and being Caucasian.[168] The above characteristics should be reported as baseline characteristics in trials to allow one to determine if the samples

were comparable at the outset for known factors. Any imbalances in the distribution of risk factors can then be accounted for in an adjusted analysis.

No trials reported ulcer duration, ulcer area at baseline and ethnicity by treatment groups. Five trials reported ulcer area,[74,105,114,119] two trials reported ulcer duration,[75,100] and four trials reported ethnicity.[108,109,114] Other trials reported baseline characteristics such as duration of diabetes, arterial blood supply (reported as a ratio of ankle and brachial systolic blood pressure to ankle brachial pressure to index, or ABPI), or Wagner grade. These may inform external validity but not be as important for determining prognosis.

Outcomes

Owing to the large number of different outcomes reported, it was considered inappropriate to synthesise results. In addition, the definitions of the outcomes used, such as 'clinical cure of infection', were not specified. There appears to be little agreement on what is the key outcome measure for assessing the effectiveness of an antimicrobial in the management of DFUs. It could be resolution of infection, healing of the ulcer, prevention of amputation (all amputations or only major amputations) or maintenance of HRQoL. The relationship between resolution of infection, ulcer healing and the need for amputation is not completely understood so we cannot be confident that an intervention which leads to quicker resolution of infection would necessarily lead also to quicker healing and hence reduce the need for amputation. In designing clinical studies, there is a need to trade off the need for an efficient use of trial resources and the desire to have a lengthy follow-up period in order to capture sufficient events of interest. However, for an outcome such as major amputation this may be prohibitively expensive, hence commoner events such as 'resolution of infection', healing or minor amputations may also be reported. A minor amputation may be considered as an outcome in itself or as a part of the therapeutic armoury – removal of an ulcerated toe, for example, may lead to dramatic improvement in a patient's quality of life, compared with, for example, sustained non-weight bearing while the ulcer heals conservatively.

It is possible that an intervention could accelerate the rate at which the infection appears 'resolved', but delay healing and increase the risk of major amputation, for example, by keeping the ulcer open for longer. Having sufficient follow-up to allow reporting all these outcomes would increase our knowledge about the relationship between infection, healing and amputation and increase our confidence in the relevance of the trials that only reported resolution of infection or healing.

It is also possible that an intervention could lead to a higher healing rate but lead to reduced HRQoL in patients – for example, having daily injections of growth factors, or dressing changes may be unacceptable for some patients owing to their effect on their normal activities. No trials reported the impact of these interventions on HRQoL.

Furthermore, an intervention might delay healing minimally compared with a comparator but reduce the chances of microbial resistance developing, e.g. MRSA, and therefore be desirable from a societal perspective. It is not clear how these two perspectives, the individual and the societal, should be weighed against each other.

A number of trials reported both 'eradication of pathogens' and 'clinical cure' data. It may be interesting to investigate the relationship between these two outcomes and eventual healing/amputation. If it were established that there was a known relationship between clinical cure and amputation or healing outcomes, then trials could be powered on this outcome and have follow-up for the length of time needed to capture clinical resolution of infection. Only group-level data were available to us and therefore we could not do this. If clinical cure and eradication of pathogens were congruent, then it may be possible to reduce the number of bacteriology swabs requested in clinical trials. If they are not in agreement, it would be interesting to see whether the false positive and false negative rate is related to the diabetes, due to sampling error or other reasons.

There is some suggestion that people with diabetes do not exhibit the same response to infection as those without diabetes owing to changes in the immune system, hence classical signs of clinical resolution of infection may not be a reliable indication for cure or for trial outcome measures.[165]

Applicability of the results

The majority of trials (17/23) had more men than women taking part, in two trials there were no data on the gender of participants, in one trial only one woman was included[101] and in three trials there were no women participating.[75,110–112]

Margolis and colleagues did not find any difference in prognosis for healing of neuropathic ulcers with gender,[168] but qualitative studies suggest that men and women adjust to life with a diabetic foot ulcer differently,[169] and this may affect the generalisability of the results from these trials.

The majority of these trials reported that they included people with neuropathic ulceration ($n = 12$),[44,74,105,107,110–112,114,118,122,124,125] or specified a minimum arterial blood supply ($n = 4$).[100,106,109,119] Four trials[43,75,108,123] did not provide information on the proportion of people with neuropathic, ischaemic or neuroischaemic ulceration. Within trials where ulcer aetiologies are provided, it is also important that the degree of neuropathy or ischaemia is described so that the relevance of the findings to other patient groups can be ascertained.

The patient characteristics may also affect the effectiveness of the intervention. A trial of antibiotics in people with neuropathic ulceration may not be applicable to patients in whom arterial supply is limited, as the delivery of this intervention relies upon sufficient arterial supply to allow the antibiotics to penetrate the tissues at a therapeutic concentration.

The majority of studies were conducted on inpatients and only one study described outpatient treatment of infected diabetic foot infection.[75] The other trials of antimicrobial agents in outpatients included people without frank ulcer infection.

Trade-offs between the benefits, harms and costs of the intervention

Administering antimicrobial agents may have harms in addition to any anticipated benefits. From an individual perspective, the use of antibiotics can lead to adverse effects ranging from relatively common stomach upsets/diarrhoea to rare and potentially fatal reactions.

From a community perspective, the administration of antibiotics to people with DFUs needs to be weighed against the increasing use of antibiotics and the association to the spread of resistance to antibiotics, for example MRSA. The general principle for reducing the spread of resistance is that broad-spectrum antibiotics should be avoided and therapy should be based on culture results. While clinical guidelines reinforce the approach of prescribing antibiotics according to bacteriology results, they also mention the need for empirical therapy in limb-threatening infection. Waiting for laboratory results is not always possible owing to the potential consequences of delay for the infection, such as amputation. Reserving antibiotic treatment for people with suspected **severe** ulcer infection might help limit the growth of resistant organisms. Developments in rapid diagnosis of infecting organisms, such as PCR or near-patient testing techniques, may permit rapid diagnosis of bacterial colonisation/infection, but we know nothing about their usefulness in wounds. If useful, this may help reduce the use of broad-spectrum antibiotics, but if the most infections are truly polymicrobial then they may still require a broad-spectrum antibiotic and therefore rapid assessment may change the therapeutic regimen in a proportion of patients.

In addition, the majority of the trials of antibiotics used a combination of two agents. It is not clear whether using multiple agents is of added benefit over single agents in the patient group. Multiple agents might lead to net benefit if, for example, two narrower spectrum agents could be used to cover the most common pathogens (*Staphylococcus aureus, Streptococcus* spp., *Pseudomonas aeruginosa* and the *anaerobes)*, but using more than one drug also puts the patient at risk of more than one set of adverse events/reactions.

In some cases the intervention regimen was very complex, involving combinations of intravenous, oral and intramuscular therapies, e.g. in the studies of Seidel and colleagues.[110–112] In some cases there were a number of additional antibiotics which could be added to the regimen under evaluation, as required, and the lack of objective criteria for the use of adjuvant therapies means that one cannot be confident that any difference in outcomes is due to the antibiotic under test.[109]

Costs of these treatments vary. The costs of antimicrobial agents range from $1.44 to $104 per day,[170] but the cost of the antimicrobial agents is usually minimal compared with the costs of delivering care such as hospitalisation and nurse's visits or the costs of interventions such as amputation.

A number of expensive interventions such as growth factors and sterile medical larval therapy are relatively new and therefore there may be a reduction in costs if more providers come on-stream, e.g. larval therapy costs around £55 per dose (only a few doses are usually needed).[171] Growth factors such as G-CSF (filgrastim) cost £540 for 7 days.[121] It is not clear if improvements in the technology to produce these would lead to a reduction in costs or whether licensing restrictions

mean that these costs would be maintained. Two studies had economic analyses alongside an effectiveness trial and two additional studies reported costs.[121,124] Further cost-effectiveness studies need to be run in parallel to effectiveness trials in order to inform decision-makers of the costs and benefits of the intervention on offer. An expensive intervention may be cost-effective if it reduces the time to healing, the rate of amputation or the number of days in hospital/clinician visits.

One important advance in reducing the costs of treatment of established infections could be in moving the setting of care from hospital to primary care. Until recently, all the antibiotics recommended for use in the treatment of limb-threatening infections were administered intravenously and therefore the patient was hospitalised. The development of oral antibiotics suitable for this population might lead to more people being treated at home, thus reducing costs to the health service. Hospitalisation not only allows antibiotics to be administered intravenously, but also permits close monitoring of diabetic control and ensuring that the patient remains non-weight bearing. Outpatient treatment therefore may not always be as effective or cost-effective if, for example, it is associated with slower healing or requires a different configuration of services to ensure close monitoring of progress. In addition, people with limb-threatening infection may be so unwell that hospitalisation is required.

Strengths and weaknesses of the review

Strengths of the review

The review strengths include the extensive electronic search strategies developed to retrieve controlled trials regardless of publication status, date or language of publication, and the examination of bibliographies of systematic and non-systematic reviews and all included studies to identify additional citations. The wide-ranging steering group, in terms of professional background and geography, also may have increased our chances of identifying unpublished, ongoing or unindexed studies in the area.

Decisions to include or exclude studies were made by two researchers independently and then resolved by discussion. We have also set out the reasons for the exclusion of 20 diagnostic studies, 140 effectiveness studies and 24 economic studies in Appendix 6. Data extraction and quality assessment were done by one person and checked by a second. These steps sought to reduce error or bias in the review process.

We enlisted a large group of collaborators to peer review the review protocol, with input from experts in many disciplines and two people with experience of diabetic foot ulceration. The steering group for the project also represents a range of disciplines and supported the reviewers throughout.

Weaknesses of the review

Weaknesses of the review process included being unable to undertake handsearching of conference proceedings beyond those listed in *Table 2* (six conferences). Research into the treatment of DFU infection is presented at conferences organised by vascular surgical societies, wound care societies, diabetologists, podiatrists, clinical microbiologists and experts in infection control. We were able to access only a small proportion of conference proceedings from these cognate areas through our collaborators and may have missed abstracts from other conferences. However, the electronic databases HELMIS and SIGLE also index some conference proceedings and therefore our searches will probably have reached other relevant conferences.

There may have been research conducted into the effect of antimicrobial agents with funding from commercial concerns and these may not be in the public domain. Given the tendency for selective reporting of research with 'positive' findings (publication bias), then it is possible that there are additional studies published in abstract format or in journals which are unindexed by the databases that we used, or indeed not published at all. What we know about publication bias leads us to suggest that if we have missed other studies, then these would tend to be small studies with 'negative' or equivocal results.[172]

Our search for studies to answer the question about the effect of microbiological analysis was confined to RCTs or CCTs, and it is possible that controlled before and after studies could have been reported in this area. Locating controlled before and after studies is not straightforward, as the search filters to identify them from electronic databases are less well developed than for, for example, RCTs. Our bibliography checking and contact with a large expert panel who were not aware of any such studies suggest that few, if any, controlled before and after studies exist.

Integration of this review with previous work

We identified two previous systematic reviews of intervention for diabetic foot ulceration[98,99] and one of the authors led a previous systematic review in this area. The reviews by Mason and colleagues[99] and Kaltenthaler and colleagues[98] included evaluation of systemic and topical antimicrobial agents within their scope. Our previous review (by O'Meara and colleagues[48]) evaluated the impact of antimicrobial agents in the healing of DFUs. In the current review we decided to include studies if they reported any of the following objective outcomes of interest:

- mortality
- ulcer recurrence
- incidence/type of amputation
- number/duration hospital admissions for DFU problems
- incidence of osteomyelitis
- bacterial profile of ulcer
- pain
- acquisition of resistant organisms
- proportion of ulcers healing
- relationship between ulcer healing and bacteriology
- time to complete healing
- change in mobility
- change in ulcer area
- change in level of dependence/independence
- healing rate
- impact on HRQoL
- change in ulcer depth or volume.

This is in contrast to the earlier review in which only studies which reported wound area/volume, time to healing, healing rate or proportion of healed outcomes were included, as we hoped that we would identify high-quality data on the effect of these interventions on outcomes that guide clinicians, such as resolution of infection, and to investigate the relationship between bacteriology and healing. We found no such research.

Decision analytic model

We were unable to identify data on the transition probabilities for our two populations of interest. These were people in whom a first course of antibiotics had failed, and people with apparently uninfected ulcers being offered antimicrobial therapy (presumably as the clinician suspects that lack of progress towards ulcer healing is due to a high bacterial load). None of the existing models provided transition probabilities for these two groups as they were designed to evaluate the impact of therapeutic interventions in either newly infected or uninfected populations. No trials stated that they recruited people for whom a first course of antibiotics had failed. A few trials involved people with apparently clinically uninfected ulcers, but these trials did not report clear criteria for the definition of recalcitrant ulceration.

We identified in interviews with six experts that people with clinically infected ulcers are almost invariably treated with antibiotics without waiting for the results of microbiological analysis and therefore the results of a diagnostic test do not inform their therapy, unless they fail to respond. Similarly, patients whose ulcers appear uninfected and are healing are not considered to require antimicrobial therapy and are not subjected to microbiological analysis. The performance of diagnostic tests (following clinical assessment) is unlikely to inform the management of these patients unless they fail to heal. Trials of antibiotics for clinically infected ulcers confirmed that treatment was decided empirically rather than after receiving the results of a microbiological test. Our experts confirmed that this was due to the danger of waiting for microbiological results and the high risk of progressive infection which could result in amputation. Diagnostic tests appear to be used to guide therapy when a clinical assessment has indicated that the ulcer, although apparently uninfected, is failing to heal (determined by a range of criteria).

A number of substitute strategies were proposed in an attempt to inform the decision analytic model. The review of the literature indicated that information regarding the populations of interest might have been collected as part of some studies, and there may have been subgroups within these studies which could have provided data on the 'hard to heal' ulcers. Although direct contact with the principal investigators of studies reporting on 'hard to heal' DFUs was considered as an option, we decided not to pursue this avenue as there was sufficient variation in the characterisation of a 'hard to heal' DFU (from our clinician interviews) to suggest that not much would be gained if access to the primary data was granted.

It is possible that non-comparative studies, such as case series, may have described these populations in sufficient detail to ascertain if individuals belonged to either of the two target groups and to provide some transition probabilities, but we were

unable to search for case series within the staff and time constraints of this project.

It can be argued that the existing evidence provided in the literature indirectly provides information about the two groups of patients that were identified as the target populations. For example, the probability of having an ulcer clear of infection after a second course of antibiotics might be a function of the probability of having an ulcer clear of infection after a first course of antibiotics and the effectiveness associated with specific antibiotics in patients with an infected foot ulcer. This can be described as a network of evidence, i.e. information about the parameters of interest could be constructed as functions of estimates reported in the literature. Statistical methods for synthesising evidence could be used to estimate indirectly the required parameters for the decision analytic model.[173] However, the human resources and the time required to conduct this type of analysis were outside the scope of this project.

Chapter 6
Conclusions

Implications for clinical practice

The available evidence is too weak to draw reliable implications for practice. This means that, in terms of diagnosis, we do not know how to identify infection reliably by clinical assessment, which patients need formal diagnostic testing for infection, whether empirical treatment with antibiotics (before the results of diagnostic tests are available) leads to better outcomes and what the optimal methods of diagnostic testing are. With respect to treatment, we do not know whether treatment with systematic or local antibiotics leads to better outcomes, or whether any particular agent is more effective. Limited evidence suggests that both G-CSF and cadexomer iodine dressings are less expensive than 'standard care', that A/S is a less costly treatment than I/C, and that an unlicensed cream (pexiganan) may be as effective as oral ofloxacin.

Implications for research

Questions to be answered

1. What characteristics of infection in people with DFU influence healing and amputation outcomes?
2. Does diagnosis of infection-producing bacteria prior to treatment offer any benefit over empirical therapy?
3. If detecting infection-producing bacteria offers clinical benefit, then what are the most effective and cost-effective methods for detecting infection, for example clinical assessment, wound swabbing or wound biopsy and microbiological analysis, or novel techniques such as electronic nose/tongue, and PCR analysis?
4. What are the relative effectiveness and cost-effectiveness of antimicrobial interventions for DFU infection, for example combinations of broad-spectrum antibiotics, larval therapy, growth factors and topical agents/dressings?

Nature of the research

- Research needs to have adequate sample sizes and robust methods to minimise bias.
- Future research should attempt to use 'real-life' methods as far as possible in order to improve the clinical applicability of findings.
- Outcomes should include pain, quality of life and acceptability associated with diagnostic procedures and interventions.
- Economic evaluations of diagnosis and antimicrobial agents should be undertaken, where possible, alongside primary studies. These should be undertaken using appropriate methods as determined by experts in health economics.
- Future research should include sufficient details of the quality of sample acquisition, laboratory procedures, concurrent therapies and outcome assessment.
- Attention should be paid to the potential for the development of resistant organisms associated with the use of long-term, broad-spectrum antibiotics and the balance of societal and individual benefit.
- Future trials should report the baseline characteristics of both patients and their wounds by study group and analysis should attempt to adjust for any imbalances in prognostic factors present at baseline.

Future trials need to be reported using CONSORT guidelines, and evaluations of diagnostic accuracy using STARD guidelines.

Information regarding the following is required to populate the decision analytic model:

- Incidence of DFU patients who have failed to heal after a first course of antibiotics and those who do not show any clinical symptoms of infection but whose ulcer is not healing (target population).
- Natural history of the target population.
- Diabetic foot ulcer recurrences in target population.
- Healthcare resource use of target population in the UK.
- Quality of life scores for the target population.
- Diagnostic performance of clinical assessments and investigations in the target population.
- Effects of different strategies or interventions for the management of DFU infection in the target population.

A register including both patient- and ulcer-level characteristics and foot ulcer and systemic treatments and outcomes may provide information

to populate the decision analytic model and serve to suggest fruitful areas of study in diagnosis, prognosis and therapeutics, in addition to providing feedback on quality of care, but it is unclear whether it would be simple to collect data on these elements in a diabetic foot register or to extend data collection in existing general diabetes registers.

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Contribution of the authors

E Andrea Nelson (Reader, health research) conceived the study, contributed to the protocol development, search strategy development and study selection. She carried out data extraction and methodological appraisal for some diagnostic studies, all clinical effectiveness studies and economic evaluations and data analysis for the effectiveness studies. She wrote the results section for effectiveness studies and economic evaluations and commented on all other sections. She was the overall supervisor and is the guarantor for the project. Susan O'Meara (Research Fellow, systematic reviews) contributed to the protocol development, search strategy development, study selection for all sections of the project and updating/maintenance of the bibliographic database. She carried out data extraction and methodological appraisal for all diagnostic studies and some of the clinical effectiveness studies and economic evaluations and data analysis for the diagnostic studies. She wrote the following sections: introduction, methods, results for diagnostic studies and discussion. She read and offered comments on the other sections. Dawn Craig (Research Fellow, health economics) and Cynthia Iglesias (Research Fellow, health economics) performed the systematic review of economic models and quality of life studies. They were also responsible for the construction of the decision analytic model and the preparation of the manuscript describing the economic component of the DASIDU project. C Iglesias (Research Fellow) reviewed the economic and utility evidence and worked on the draft of the economic section of the report. Su Golder (Information Officer, literature searching) devised search strategies, carried out literature searches and wrote part of the methodology and Appendix 1. Jane Dalton (Reviewer, systematic reviews) undertook handsearching, assessed papers for inclusion and contacted authors. She carried out data extraction and quality assessment of papers, data analysis and drafting report section for effectiveness results. She also commented on the final version of the report. Karl Claxton (Senior Lecturer, health economics) provided expert advice on the construction of the decision analytic model and commented on previous versions of the economic section of this report. Sally Bell-Syer (Research Fellow, systematic reviews) contributed to the protocol development and search strategy development. She read and offered comments on all sections of the report. Edward Jude (Consultant Physician, diabetes care) contributed to the analysis of clinical data and commented on the draft report. Christopher Dowson (Professor, microbiology) contributed to the protocol development, analysis and interpretation of microbiological sections of the report, and read and commented on the draft report. Roger Gadsby (Senior Clinical Lecturer, primary care) contributed to the protocol development, interpretation of outcome data, and commented on the draft report. Paul O'Hare (Honorary Senior Lecturer, medicine) contributed to the protocol and commented on the draft report. Janet Powell (Visiting Professor, vascular surgery) contributed to the development of the protocol, and the interpretation of the clinical data, and also commented on the final draft report.

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Appendix 1

Search strategies

Clinical effectiveness search strategies

Internal CRD administration databases

The Database of Abstracts of Reviews of Effectiveness (DARE) and the Health Technology Assessment (HTA) Database
(searched: 12 November 2002)

The Database of Abstracts of Reviews of Effectiveness (DARE) and Health Technology Assessment (HTA) Database were searched via the NHS CRD's internal administration databases. This provides more detailed and more up-to-date versions of the databases than those on the Cochrane Library or the Internet and includes additional records to those in the public databases. The same search strategy was used for both databases;

1. S (neuroisch?emic or isch?emic or diabetic or neuropathic)(3w)(foot or feet or ulcer$)
2. S (pedal or plantar or foot or feet or heel)(3w)(ulcer$ or septic or wound$)
3. S (foot or feet)(6w)diabet$
4. S deep foot infection$
5. S (crural or leg)(5w)ulcer$
6. S (venous or stasis or varicos*)(5w)(leg or ulcer$)
7. S (lower extremit$ or lower limb$)(5w)(ulcer$ or wound$)
8. S s1 or s2 or s3 or s4 or s5 or s6 or s7

This identified 154 DARE records and 20 HTA records.

Internet databases

(Allied And Complementary Medicine) AMED (1985–2002 November)
(searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. exp Acetic Acid/
2. (acetic acid$ or acetate$ or acetamide$ or acetoxyacetylaminofluorene$ or hydroxyacetylaminofluorene$ or allylisopropylacetamide$).ti,ab.
3. (idoacetamide$ or idoacetate$ or piracetam$ or thioacetamide$ or gadolinium$ or technetium$ or dichoroacetate$ or fluoroacetate$ or iodoacetate$).ti,ab.
4. (foscarnet$ or thioglycolate$ or acetic anhydride$).ti,ab.
5. ((aminooxyacetic or edetic or egtazic or iodoacetic or nitrilotriacetic or pentetic or peracetic or phosphonoacetic or trichloroacetic or trifluoroacetic) adj acid$).ti,ab.
6. (therapeutic fungicide$ or antifungal agent$ or antifungals).ti,ab.
7. (benzoate$ or butenafine$ or chlorquinaldol$ or cyclosporine$ or dichlorophen$ or fluconazole$ or flucytosine$ or glycyrrhizic acid$ or hexetidine$ or itraconazole$ or monensin$ or nifuratel$ or pentamidine$).ti,ab.
8. (co-amoxiclav$ or sodium benzoate$ or thimerosal$ or thiram$ or thymol$ or tolnaftate$ or tomatine$ or triacetin$ or trimetrexate$).ti,ab.
9. (amoroldine$ or benzoic acid$ or clotrimazole$ or econazole$ or ketoconazole$ or miconazole$ or nystatin$ or Salicylic acid$ or sulconazole$ or terbinafine$ or tioconazole$ or undecenoate$).ti,ab.
10. (antiviral$ or anti viral$ or idoxuridine$).ti,ab.
11. (acetylcysteine$ or acyclovir$ or amantadine$ or aphidicolin$ or aprotinin$ or brefeldin or bromodeoxyuridine$ or cytarabine$ or deoxyglucose$ or dextran sulfate$).ti,ab.
12. (dideoxyadenosine$ or dideoxynucleoside$ or dihematoporphyrin ether$ or ditiocarb$ or filipin$ or floxuridine$ or ganciclovir$ or inosine pranobex or interferon alfa$ or interferon type$ or interferon beta or interferon gamma or interferons).ti,ab.
13. (methisazone$ or phosphonoacetic acid$ or poly a-u or poly i-c or pyran copolymer$ or ribavirin$ or rimantadine$ or streptovaricin$ or tenuazonic acid$ or tilorone$ or trifluridine$ or tunicamycin$ or vidarabine$).ti,ab.
14. (bacitracin$ or povidone iodine$ or betaisodona$ or polyvinylpyrrolidone iodine$ or betadine$ or disadine$ or isodine$ or pvp-i or pharmadine$).ti,ab.
15. (cetyltrimethylammonium or cetrimide$ or cetrimonium).ti,ab.
16. (chlorate$ or cisplatin or hydrochloric acid$ or chloride$ or hypochlorous acid$ or hypochlorite$ or perchloric acid$ or ruthenium red$).ti,ab.

17. exp "Eosine Yellowish-(YS)"/
18. (eusol or phenoxyethanol$ or dextranomer$ or framycetin sulphate$ or mandelic acid$ or tetrabromofluorescein$ or eosin or eosine or chlortetracycline$ or chloroxylenol solution$).ti,ab.
19. (edinburgh adj university adj solution adj2 lime).ti,ab.
20. (cyclandelate$ or vanilmandelic acid$).ti,ab.
21. hexachloroph#ne$.ti,ab.
22. (triclosan$ or polymyxin$ or polynoxylin$).ti,ab.
23. (silver adj2 dressing$).ti,ab.
24. (gentian violet or crystal violet or methyl violet or methylrosaniline chloride$ or hexamethylpararosanine chloride$).ti,ab.
25. (potassium permanganate$ or permanganic acid$ or potassium salt$).ti,ab.
26. (mupirocin$ or pseudomonic acid$ or bactroban$).ti,ab.
27. (neomycin$ or fradiomycin$ or neamin$).ti,ab.
28. (benzyol peroxide$ or benzyol superoxide$ or diphenylglyoxal superoxide$ or panoxyl$).ti,ab.
29. exp Hydrogen Peroxide/
30. (hydrogen peroxide$ or hydroperoxide$ or oxydol$ or perhydrol$ or superoxol$ or diphenylglyoxal superoxide$ or panoxyl$).ti,ab.
31. (fucithalmic$ or fusidate$ or fusidin$ or stanicide$).ti,ab.
32. (liposome$ adj hydrogel$).ti,ab.
33. (fusidic acid$ or inadine$ or betadine$).ti,ab.
34. (cadexomer iodine$ or chlorhexidine$ or novalsan$ or sebidin$ or tubulicid$).ti,ab.
35. exp Larva/
36. (maggot$ or larva or larvae or larval).ti,ab.
37. exp Complementary Therapies/
38. (plant extract$ or aromatherap$ or marigold extract$ or calendula officinalis or tagetes patula or rubia cordifolia or manjishtha or withania somnifera or ashvagandha).ti,ab.
39. exp Plant Extracts/
40. exp Plants, Medicinal/
41. (phytotherapy or cascara$ or curare$ or chinese herb$ or guaiac$ or ipecac$ or podophyll$ or psyllium$ or senna extract$ or tragacanth$ or turpentine$).ti,ab.
42. exp oils, volatile/ or exp plant oils/
43. exp Sucrose/
44. exp HONEY/
45. (essential oil$ or plant oil$ or tea tree or lavender or chamomile or camomile or rosemary).ti,ab.
46. (sucrose or sugar paste$ or granulated sugar).ti,ab.
47. exp Propolis/
48. (propolis or honey or beebread$ or bee bread$ or bee glue$).ti,ab.
49. exp Antiviral Agents/
50. (disinfect$ or antisept$ or anti-sept$ or antiviral$ or anti-viral$).ti,ab.
51. ((neuroisch?emic or isch?emic or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).ti,ab.
52. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
53. ((foot or feet) adj6 diabet$).ti,ab.
54. deep foot infection$.ti,ab.
55. exp Foot Ulcer/
56. or/51-55
57. Leg Ulcer/
58. Varicose Ulcer/
59. ((crural or leg) adj5 ulcer$).ti,ab.
60. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).ti,ab.
61. ((venous or stasis or leg) adj5 wound$).ti.
62. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).ti,ab.
63. or/57-62
64. 56 or 63
65. (penicillin$ or amdinocillin$ or amox#cillin$ or ampicillin$ or azlocillin$).ti,ab.
66. (carbenicillin$ or carfecillin$ or cloxacillin$ or dicloxacillin$ or floxacillin$ or flucloxacillin$ or methicillin$ or mazlocillin$ or nafcillin$ or oxacillin$ or penicillanic acid$).ti,ab.
67. (penicillic acid$ or phenoxymethylpenicillin$ or piperacillin$ or pivampicillin$ or sulbencillin$ or talampicillin$ or sultamicillin$ or ticarcillin$ or ticercillin$).ti,ab.
68. (cefaclor$ or cefadroxil$ or cefalexin$ or cefazolin$ or cefamandole$ or cefixime$ or cefotaxime$ or cefoxitin$ or cefpirome$ or cefpodoxime$ or cefprozil$).ti,ab.
69. (cefradine$ or ceftazidime$ or ceftizoxime$ or ceftriaxone$ or cefuroxime$).ti,ab.
70. (cefonicid$ or cefmenoxine$ or cefoperazone$ or cefotiam$ or cefsulodin$ or cephacetrile$ or cephalexin$ or cephaloglycin$ or cephaloridine or cephalosporanic acid$ or cephalothin$ or cephapirin$ or cephradine$).ti,ab.
71. (beta lactam$ or aztreonam$ or cilastin$ or imipenem$ or meropenem$ or sulbactam$ or tazobactam$).ti,ab.
72. (caprolactam$ or clavulan$ or moxalactam$).ti,ab.
73. (Aminoglycoside$ or anthracycline$ or aclarubicin$ or daunorubicin$ or carubicin$ or doxorubicin$ or epirubicin$ or idarubicin$ or nogalamycin$ or menogaril$ or plicamycin$).ti,ab.
74. (gentamicin$ or neomycin$ or netilmicin$ or tobramycin$).ti,ab.

75. (amphotericin$ or antimycin$ or candicidin$ or roxithromycin$ or josamycin$ or leucomycin$ or kitasamycin$ or lucensomycin$ or maytansine$ or mepartricin$ or miocamycin$).ti,ab.
76. (natamycin$ or oleandomycin$ or troleandomycin$ or oligomycin$ or rutamycin$ or sirolimus$ or tacrolimus$ or tylosin$ or propiolactone$ or spironolactone$ or venturicidin$ or zearalenone$ or zeranol$).ti,ab.
77. (azithromycin$ or clarithromycin$ or erythromycin$ or spiramycin$).ti,ab.
78. (moxifloxacin$ or quinolone$ or ciprofloxacin$ or clinafloxacin$ or fluoroquinolone$ or levofloxacin$ or ofloxacin$).ti,ab.
79. (fleroxacin$ or enoxacin$ or norfloxacin$ or pefloxacin$ or nalidixic acid$ or nedocromil$ or oxolinic acid$ or quinpirole$ or quipazine$ or saquinavir$).ti,ab.
80. (dmso or sulfoxide$ or sulphoxide$ or sulfonamide$ or sulphonamide$ or trimethoprim$ or sulfamethoxazole$ or sulphamethoxazole$ or co-trimoxazole$ or sulfadiazine$ or sulphadiazine$ or sulfametopyrazine$ or sulfalene$ or sulphametopyrazine$ or sulphalene$).ti,ab.
81. (benzolamide$ or bumetanide$ or chloramine$ or chlorthalidone$ or clopamide$ or dichlorphenamide$ or ethoxzolamide$ or indapamide$ or mafenide$ or mefruside$ or metolazone$ or prodenecid$ or sulfanilamide$ or sulphanilamide$ or furosemide$ or sulfacetamide$ or sulphacetamide$).ti,ab.
82. (sulfachlorpyridazine$ or sulfadimethoxine$ or sulfadoxine$ or sulfaguanidine$ or sulfamerazine$ or sulfameter$ or sulfamethazine$ or sulfamethoxypyridazine$ or sulphachlorpyridazine$ or sulphadimethoxine$ or sulphadoxine$ or sulphaguanidine$ or sulphamerazine$ or sulphameter$ or sulphamethazine$ or sulphamethoxypyridazine$).ti,ab.
83. (sulfamonomethoxine$ or sulfamoxole$ or sulfaphenazole$ or sulfapyridine$ or sulfaquinoxaline$ or sulfathiazole$ or sulfamethizole$ or sulfisomidine$ or sulfisoxazole$ or sulfasalazine$ or sumatriptan$ or xipamide$ or thioamide$ or thioacetamide$ or sulphamonomethoxine$ or sulphamoxole$ or sulphaphenazole$ or sulphapyridine$ or sulphaquinoxaline$ or sulphathiazole$ or sulphamethizole$ or sulphisomidine$ or sulphisoxazole$ or sulphasalazine$).ti,ab.
84. (tetracycline$ or demeclocycline$ or doxycycline$ or lymecycline$ or minocycline$ or oxytetracycline$).ti,ab.
85. (chlortetracycline$ or methacycline$ or rolitetracycline$).ti,ab.
86. (cloranfenicol$ or chloramphenicol$).ti,ab.
87. (thiamphenicol$ or kloramfenikol$ or levomycetin$ or chlornitromycin$ or chlorocid$ or chloromycetin$ or detreomycin$ or ophthochlor$ or syntomycin$).ti,ab.
88. (clindamycin$ or dalacin c or cleocin$ or chlo?lincocin$).ti,ab.
89. (linezolid$ or trivazol$ or vagilen$ or clont$ or danizol$ or fagyl$ or ginefavir$ or metrogel$ or metrodzhil$ or satric$ or trichazol$ or trichopol$).ti,ab.
90. (granulocyte colony stimulating factor or gcsf or ozone).ti,ab.
91. (fusidate$ adj (sodium or silver)).ti,ab.
92. (antibiotic$ or antimicrobial$).ti,ab.
93. (griseofulvin or synercid or dalfopristin or quinupristin).ti,ab.
94. exp Complementary medicine/
95. exp antiinfective agents/
96. or/1-50
97. or/65-95
98. 64 and (96 or 97)

This identified 49 records.

British Nursing Index (BNI) (1994–2002 August) (searched: 6 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. (clinical trial$ or random$ or placebo$ or control or controls or controlled).mp.
2. (single blind$ or double blind$ or trebl$ blind$ or tripl$ blind$).mp.
3. (meta-analys$ or meta analys$ or comparison group or standard treatment$ or systematic review$).mp.
4. (acetic acid$ or acetate$ or acetamide$ or acetoxyacetylaminofluorene$ or hydroxyacetylaminofluorene$ or allylisopropylacetamide$).mp.
5. (idoacetamide$ or idoacetate$ or piracetam$ or thioacetamide$ or gadolinium$ or technetium$ or dichoroacetate$ or fluoroacetate$ or iodoacetate$).mp.
6. (foscarnet$ or thioglycolate$ or acetic anhydride$).mp.
7. ((aminooxyacetic or edetic or egtazic or iodoacetic or nitrilotriacetic or pentetic or peracetic or phosphonoacetic or trichloroacetic or trifluoroacetic) adj acid$).mp.
8. (therapeutic fungicide$ or antifungal agent$ or antifungals).mp.

9. (benzoate$ or butenafine$ or chlorquinaldol$ or cyclosporine$ or dichlorophen$ or fluconazole$ or flucytosine$ or glycyrrhizic acid$ or hexetidine$ or itraconazole$ or monensin$ or nifuratel$ or pentamidine$).mp.
10. (co-amoxiclav$ or sodium benzoate$ or thimerosal$ or thiram$ or thymol$ or tolnaftate$ or tomatine$ or triacetin$ or trimetrexate$).mp.
11. (amoroldine$ or benzoic acid$ or clotrimazole$ or econazole$ or ketoconazole$ or miconazole$ or nystatin$ or Salicylic acid$ or sulconazole$ or terbinafine$ or tioconazole$ or undecenoate$).mp.
12. (antiviral$ or anti viral$ or idoxuridine$).mp.
13. (acetylcysteine$ or acyclovir$ or amantadine$ or aphidicolin$ or aprotinin$ or brefeldin or bromodeoxyuridine$ or cytarabine$ or deoxyglucose$ or dextran sulfate$).mp.
14. (dideoxyadenosine$ or dideoxynucleoside$ or dihematoporphyrin ether$ or ditiocarb$ or filipin$ or floxuridine$ or ganciclovir$ or inosine pranobex or interferon alfa$ or interferon type$ or interferon beta or interferon gamma or interferons).mp.
15. (methisazone$ or phosphonoacetic acid$ or poly a-u or poly i-c or pyran copolymer$ or ribavirin$ or rimantadine$ or streptovaricin$ or tenuazonic acid$ or tilorone$ or trifluridine$ or tunicamycin$ or vidarabine$).mp.
16. (bacitracin$ or povidone iodine$ or betaisodona$ or polyvinylpyrrolidone iodine$ or betadine$ or disadine$ or isodine$ or pvp-i or pharmadine$).mp.
17. (cetyltrimethylammonium or cetrimide$ or cetrimonium).mp.
18. (chlorate$ or cisplatin or hydrochloric acid$ or chloride$ or hypochlorous acid$ or hypochlorite$ or perchloric acid$ or ruthenium red$).mp.
19. (eusol or phenoxyethanol$ or dextranomer$ or framycetin sulphate$ or mandelic acid$ or tetrabromofluorescein$ or eosin or eosine or chlortetracycline$ or chloroxylenol solution$).mp.
20. (edinburgh adj university adj solution adj2 lime).mp.
21. (cyclandelate$ or vanilmandelic acid$).mp.
22. hexachloroph#ne$.mp.
23. (triclosan$ or polymyxin$ or polynoxylin$).mp.
24. (silver adj2 dressing$).mp.
25. (gentian violet or crystal violet or methyl violet or methylrosaniline chloride$ or hexamethylpararosanine chloride$).mp.
26. (potassium permanganate$ or permanganic acid$ or potassium salt$).mp.
27. (mupirocin$ or pseudomonic acid$ or bactroban$).mp.
28. (neomycin$ or fradiomycin$ or neamin$).mp.
29. (benzyol peroxide$ or benzyol superoxide$ or diphenylglyoxal superoxide$ or panoxyl$).mp.
30. (hydrogen peroxide$ or hydroperoxide$ or oxydol$ or perhydrol$ or superoxol$ or diphenylglyoxal superoxide$ or panoxyl$).mp.
31. (fucithalmic$ or fusidate$ or fusidin$ or stanicide$).mp.
32. (liposome$ adj hydrogel$).mp.
33. (fusidic acid$ or inadine$ or betadine$).mp.
34. (cadexomer iodine$ or chlorhexidine$ or novalsan$ or sebidin$ or tubulicid$).mp.
35. exp Larva/
36. (maggot$ or larva or larvae or larval).mp.
37. exp alternative medicine/
38. (plant extract$ or aromatherap$ or marigold extract$ or calendula officinalis or tagetes patula or rubia cordifolia or manjishtha or withania somnifera or ashvagandha).mp.
39. (phytotherapy or cascara$ or curare$ or chinese herb$ or guaiac$ or ipecac$ or podophyll$ or psyllium$ or senna extract$ or tragacanth$ or turpentine$).mp.
40. (essential oil$ or plant oil$ or tea tree or lavender or chamomile or camomile or rosemary).mp.
41. (sucrose or sugar paste$ or granulated sugar).mp.
42. (propolis or honey or beebread$ or bee bread$ or bee glue$).mp.
43. (disinfect$ or antisept$ or anti-sept$ or antiviral$ or anti-viral$).mp.
44. ((neuroisch?emic or isch?emic or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).mp.
45. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).mp.
46. ((foot or feet) adj6 diabet$).mp.
47. deep foot infection$.mp.
48. Leg Ulcer/
49. ((crural or leg) adj5 ulcer$).mp.
50. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).mp.
51. ((venous or stasis or leg) adj5 wound$).mp.
52. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).mp.
53. (penicillin$ or amdinocillin$ or amox#cillin$ or ampicillin$ or azlocillin$).mp.
54. (carbenicillin$ or carfecillin$ or cloxacillin$ or dicloxacillin$ or floxacillin$ or flucloxacillin$ or methicillin$ or mazlocillin$ or nafcillin$ or oxacillin$ or penicillanic acid$).mp.
55. (penicillic acid$ or phenoxymethylpenicillin$ or piperacillin$ or pivampicillin$ or

sulbencillin$ or talampicillin$ or sultamicillin$ or ticarcillin$ or ticercillin$).mp.
56. (cefaclor$ or cefadroxil$ or cefalexin$ or cefazolin$ or cefamandole$ or cefixime$ or cefotaxime$ or cefoxitin$ or cefpirome$ or cefpodoxime$ or cefprozil$).mp.
57. (cefradine$ or ceftazidime$ or ceftizoxime$ or ceftriaxone$ or cefuroxime$).mp.
58. (cefonicid$ or cefmenoxine$ or cefoperazone$ or cefotiam$ or cefsulodin$ or cephacetrile$ or cephalexin$ or cephaloglycin$ or cephaloridine or cephalosporanic acid$ or cephalothin$ or cephapirin$ or cephradine$).mp.
59. (beta lactam$ or aztreonam$ or cilastin$ or imipenem$ or meropenem$ or sulbactam$ or tazobactam$).mp.
60. (caprolactam$ or clavulan$ or moxalactam$).mp.
61. (Aminoglycoside$ or anthracycline$ or aclarubicin$ or daunorubicin$ or carubicin$ or doxorubicin$ or epirubicin$ or idarubicin$ or nogalamycin$ or menogaril$ or plicamycin$).mp.
62. (gentamicin$ or neomycin$ or netilmicin$ or tobramycin$).mp.
63. exp Macrolide/
64. (amphotericin$ or antimycin$ or candicidin or roxithromycin$ or josamycin$ or leucomycin$ or kitasamycin$ or lucensomycin$ or maytansine$ or mepartricin$ or miocamycin$).mp.
65. (natamycin$ or oleandomycin$ or troleandomycin$ or oligomycin$ or rutamycin$ or sirolimus$ or tacrolimus$ or tylosin$ or propiolactone$ or spironolactone$ or venturicidin$ or zearalenone$ or zeranol$).mp.
66. (azithromycin$ or clarithromycin$ or erythromycin$ or spiramycin$).mp.
67. (moxifloxacin$ or quinolone$ or ciprofloxacin$ or clinafloxacin$ or fluoroquinolone$ or levofloxacin$ or ofloxacin$).mp.
68. (fleroxacin$ or enoxacin$ or norfloxacin$ or pefloxacin$ or nalidixic acid$ or nedocromil$ or oxolinic acid$ or quinpirole$ or quipazine$ or saquinavir$).mp.
69. (dmso or sulfoxide$ or sulphoxide$ or sulfonamide$ or sulphonamide$ or trimethoprim$ or sulfamethoxazole$ or sulphamethoxazole$ or co-trimoxazole$ or sulfadiazine$ or sulphadiazine$ or sulfametopyrazine$ or sulfalene$ or sulphametopyrazine$ or sulphalene$).mp.
70. (benzolamide$ or bumetanide$ or chloramine$ or chlorthalidone$ or clopamide$ or dichlorphenamide$ or ethoxzolamide$ or indapamide$ or mafenide$ or mefruside$ or metolazone$ or prodenecid$ or sulfanilamide$ or sulphanilamide$ or furosemide$ or sulfacetamide$ or sulphacetamide$).mp.
71. (sulfachlorpyridazine$ or sulfadimethoxine$ or sulfadoxine$ or sulfaguanidine$ or sulfamerazine$ or sulfameter$ or sulfamethazine$ or sulfamethoxypyridazine$ or sulphachlorpyridazine$ or sulphadimethoxine$ or sulphadoxine$ or sulphaguanidine$ or sulphamerazine$ or sulphameter$ or sulphamethazine$ or sulphamethoxypyridazine$).mp.
72. (sulfamonomethoxine$ or sulfamoxole$ or sulfaphenazole$ or sulfapyridine$ or sulfaquinoxaline$ or sulfathiazole$ or sulfamethizole$ or sulfisomidine$ or sulfisoxazole$ or sulfasalazine$ or sumatriptan$ or xipamide$ or thioamide$ or thioacetamide$ or sulphamonomethoxine$ or sulphamoxole$ or sulphaphenazole$ or sulphapyridine$ or sulphaquinoxaline$ or sulphathiazole$ or sulphamethizole$ or sulphisomidine$ or sulphisoxazole$ or sulphasalazine$).mp.
73. (tetracycline$ or demeclocycline$ or doxycycline$ or lymecycline$ or minocycline$ or oxytetracycline$).mp.
74. (chlortetracycline$ or methacycline$ or rolitetracycline$).mp.
75. (cloranfenicol$ or chloramphenicol$).mp.
76. (thiamphenicol$ or kloramfenikol$ or levomycetin$ or chlornitromycin$ or chlorocid$ or chloromycetin$ or detreomycin$ or ophthochlor$ or syntomycin$).mp.
77. (clindamycin$ or dalacin c or cleocin$ or chlo?lincocin$).mp.
78. (linezolid$ or trivazol$ or vagilen$ or clont$ or danizol$ or fagyl$ or ginefavir$ or metrogel$ or metrodzhil$ or satric$ or trichazol$ or trichopol$).mp.
79. (granulocyte colony stimulating factor or gcsf or ozone).mp.
80. (fusidate$ adj (sodium or silver)).mp.
81. (antibiotic$ or antimicrobial$).mp.
82. (griseofulvin or synercid or dalfopristin or quinupristin).mp.
83. exp microbiology/
84. exp Drug Therapy/
85. or/4-43
86. (or/4-43) or (or/53-84)
87. or/44-52
88. or/1-3
89. (87 and 86) or (87 and 88)

This identified 67 records.

CINAHL (1982–2002 October, week 4) (searched: 6 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. exp clinical trials/ or random assignment/ or placebos/ or meta analysis/ or exp prospective studies/
2. systematic review/ or comparative studies/ or clinical trial.pt. or review.pt. or systematic review.pt.
3. (clinical adj trial$).ti,ab.
4. ((singl$ or doubl$ or trebl$ or tripl$) adj blind$).ti,ab.
5. (control or controls or controlled or controlling or metaanalys$).ti,ab.
6. (meta adj analys$).ti,ab.
7. (random$ or prospective$ or (comparison adj group$) or (standard adj treatment$)).ti,ab.
8. (placebo$ or (systematic adj review$)).ti,ab.
9. or/1-8
10. exp Acetic Acid/
11. (acetic acid$ or acetate$ or acetamide$ or acetoxyacetylaminofluorene$ or hydroxyacetylaminofluorene$ or allylisopropylacetamide$).ti,ab.
12. (idoacetamide$ or idoacetate$ or piracetam$ or thioacetamide$ or gadolinium$ or technetium$ or dichoroacetate$ or fluoroacetate$ or iodoacetate$).ti,ab.
13. (foscarnet$ or thioglycolate$ or acetic anhydride$).ti,ab.
14. ((aminooxyacetic or edetic or egtazic or iodoacetic or nitrilotriacetic or pentetic or peracetic or phosphonoacetic or trichloroacetic or trifluoroacetic) adj acid$).ti,ab.
15. (therapeutic fungicide$ or antifungal agent$ or antifungals).ti,ab.
16. (benzoate$ or butenafine$ or chlorquinaldol$ or cyclosporine$ or dichlorophen$ or fluconazole$ or flucytosine$ or glycyrrhizic acid$ or hexetidine$ or itraconazole$ or monensin$ or nifuratel$ or pentamidine$).ti,ab.
17. (co-amoxiclav$ or sodium benzoate$ or thimerosal$ or thiram$ or thymol$ or tolnaftate$ or tomatine$ or triacetin$ or trimetrexate$).ti,ab.
18. (amoroldine$ or benzoic acid$ or clotrimazole$ or econazole$ or ketoconazole$ or miconazole$ or nystatin$ or Salicylic acid$ or sulconazole$ or terbinafine$ or tioconazole$ or undecenoate$).ti,ab.
19. (antiviral$ or anti viral$ or idoxuridine$).ti,ab.
20. (acetylcysteine$ or acyclovir$ or amantadine$ or aphidicolin$ or aprotinin$ or brefeldin or bromodeoxyuridine$ or cytarabine$ or deoxyglucose$ or dextran sulfate$).ti,ab.
21. (dideoxyadenosine$ or dideoxynucleoside$ or dihematoporphyrin ether$ or ditiocarb$ or filipin$ or floxuridine$ or ganciclovir$ or inosine pranobex or interferon alfa$ or interferon type$ or interferon beta or interferon gamma or interferons).ti,ab.
22. (methisazone$ or phosphonoacetic acid$ or poly a-u or poly i-c or pyran copolymer$ or ribavirin$ or rimantadine$ or streptovaricin$ or tenuazonic acid$ or tilorone$ or trifluridine$ or tunicamycin$ or vidarabine$).ti,ab.
23. exp BACITRACIN/
24. (bacitracin$ or povidone iodine$ or betaisodona$ or polyvinylpyrrolidone iodine$ or betadine$ or disadine$ or isodine$ or pvp-i or pharmadine$).ti,ab.
25. (cetyltrimethylammonium or cetrimide$ or cetrimonium).ti,ab.
26. exp Chloride Compounds/
27. (chlorate$ or cisplatin or hydrochloric acid$ or chloride$ or hypochlorous acid$ or hypochlorite$ or perchloric acid$ or ruthenium red$).ti,ab.
28. (eusol or phenoxyethanol$ or dextranomer$ or framycetin sulphate$ or mandelic acid$ or tetrabromofluorescein$ or eosin or eosine or chlortetracycline$ or chloroxylenol solution$).ti,ab.
29. (edinburgh adj university adj solution adj2 lime).ti,ab.
30. (cyclandelate$ or vanilmandelic acid$).ti,ab.
31. hexachloroph#ne$.ti,ab.
32. (triclosan$ or polymyxin$ or polynoxylin$).ti,ab.
33. (silver adj2 dressing$).ti,ab.
34. (gentian violet or crystal violet or methyl violet or methylrosaniline chloride$ or hexamethylpararosanine chloride$).ti,ab.
35. (potassium permanganate$ or permanganic acid$ or potassium salt$).ti,ab.
36. exp Mupirocin/
37. (mupirocin$ or pseudomonic acid$ or bactroban$).ti,ab.
38. exp Neomycin/
39. (neomycin$ or fradiomycin$ or neamin$).ti,ab.
40. (benzyol peroxide$ or benzyol superoxide$ or diphenylglyoxal superoxide$ or panoxyl$).ti,ab.
41. exp Hydrogen Peroxide/
42. (hydrogen peroxide$ or hydroperoxide$ or oxydol$ or perhydrol$ or superoxol$ or diphenylglyoxal superoxide$ or panoxyl$).ti,ab.

43. (fucithalmic$ or fusidate$ or fusidin$ or stanicide$).ti,ab.
44. (liposome$ adj hydrogel$).ti,ab.
45. (fusidic acid$ or inadine$ or betadine$).ti,ab.
46. (cadexomer iodine$ or chlorhexidine$ or novalsan$ or sebidin$ or tubulicid$).ti,ab.
47. exp Larva/
48. (maggot$ or larva or larvae or larval).ti,ab.
49. exp alternative Therapies/
50. (plant extract$ or aromatherap$ or marigold extract$ or calendula officinalis or tagetes patula or rubia cordifolia or manjishtha or withania somnifera or ashvagandha).ti,ab.
51. exp Plant Extracts/
52. exp Plants, Medicinal/
53. (phytotherapy or cascara$ or curare$ or chinese herb$ or guaiac$ or ipecac$ or podophyll$ or psyllium$ or senna extract$ or tragacanth$ or turpentine$).ti,ab.
54. exp plant oils/
55. exp Sucrose/
56. exp HONEY/
57. (essential oil$ or plant oil$ or tea tree or lavender or chamomile or camomile or rosemary).ti,ab.
58. (sucrose or sugar paste$ or granulated sugar).ti,ab.
59. (propolis or honey or beebread$ or bee bread$ or bee glue$).ti,ab.
60. exp Anti-Infective Agents/
61. (disinfect$ or antisept$ or anti-sept$ or antiviral$ or anti-viral$).ti,ab.
62. ((neuroisch?emic or isch?emic or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).ti,ab.
63. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
64. ((foot or feet) adj6 diabet$).ti,ab.
65. deep foot infection$.ti,ab.
66. exp Foot Ulcer/
67. or/62-66
68. Leg Ulcer/
69. venous Ulcer/
70. ((crural or leg) adj5 ulcer$).ti,ab.
71. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).ti,ab.
72. ((venous or stasis or leg) adj5 wound$).ti.
73. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).ti,ab.
74. or/68-73
75. 67 or 74
76. (penicillin$ or amdinocillin$ or amox#cillin$ or ampicillin$ or azlocillin$).ti,ab.
77. (carbenicillin$ or carfecillin$ or cloxacillin$ or dicloxacillin$ or floxacillin$ or flucloxacillin$ or methicillin$ or mazlocillin$ or nafcillin$ or oxacillin$ or penicillanic acid$).ti,ab.
78. (penicillic acid$ or phenoxymethylpenicillin$ or piperacillin$ or pivampicillin$ or sulbencillin$ or talampicillin$ or sultamicillin$ or ticarcillin$ or ticercillin$).ti,ab.
79. (cefaclor$ or cefadroxil$ or cefalexin$ or cefazolin$ or cefamandole$ or cefixime$ or cefotaxime$ or cefoxitin$ or cefpirome$ or cefpodoxime$ or cefprozil$).ti,ab.
80. (cefradine$ or ceftazidime$ or ceftizoxime$ or ceftriaxone$ or cefuroxime$).ti,ab.
81. (cefonicid$ or cefmenoxine$ or cefoperazone$ or cefotiam$ or cefsulodin$ or cephacetrile$ or cephalexin$ or cephaloglycin$ or cephaloridine or cephalosporanic acid$ or cephalothin$ or cephapirin$ or cephradine$).ti,ab.
82. (beta lactam$ or aztreonam$ or cilastin$ or imipenem$ or meropenem$ or sulbactam$ or tazobactam$).ti,ab.
83. (caprolactam$ or clavulan$ or moxalactam$).ti,ab.
84. exp Aminoglycosides/
85. (Aminoglycoside$ or anthracycline$ or aclarubicin$ or daunorubicin$ or carubicin$ or doxorubicin$ or epirubicin$ or idarubicin$ or nogalamycin$ or menogaril$ or plicamycin$).ti,ab.
86. (gentamicin$ or neomycin$ or netilmicin$ or tobramycin$).ti,ab.
87. (amphotericin$ or antimycin$ or candicidin$ or roxithromycin$ or josamycin$ or leucomycin$ or kitasamycin$ or lucensomycin$ or maytansine$ or mepartricin$ or miocamycin$).ti,ab.
88. (natamycin$ or oleandomycin$ or troleandomycin$ or oligomycin$ or rutamycin$ or sirolimus$ or tacrolimus$ or tylosin$ or propiolactone$ or spironolactone$ or venturicidin$ or zearalenone$ or zeranol$).ti,ab.
89. (azithromycin$ or clarithromycin$ or erythromycin$ or spiramycin$).ti,ab.
90. (moxifloxacin$ or quinolone$ or ciprofloxacin$ or clinafloxacin$ or fluoroquinolone$ or levofloxacin$ or ofloxacin$).ti,ab.
91. (fleroxacin$ or enoxacin$ or norfloxacin$ or pefloxacin$ or nalidixic acid$ or nedocromil$ or oxolinic acid$ or quinpirole$ or quipazine$ or saquinavir$).ti,ab.
92. exp Trimethoprim/
93. (dmso or sulfoxide$ or sulphoxide$ or sulfonamide$ or sulphonamide$ or trimethoprim$ or sulfamethoxazole$ or

sulphamethoxazole$ or co-trimoxazole$ or sulfadiazine$ or sulphadiazine$ or sulfametopyrazine$ or sulfalene$ or sulphametopyrazine$ or sulphalene$).ti,ab.
94. (benzolamide$ or bumetanide$ or chloramine$ or chlorthalidone$ or clopamide$ or dichlorphenamide$ or ethoxzolamide$ or indapamide$ or mafenide$ or mefruside$ or metolazone$ or prodenecid$ or sulfanilamide$ or sulphanilamide$ or furosemide$ or sulfacetamide$ or sulphacetamide$).ti,ab.
95. (sulfachlorpyridazine$ or sulfadimethoxine$ or sulfadoxine$ or sulfaguanidine$ or sulfamerazine$ or sulfameter$ or sulfamethazine$ or sulfamethoxypyridazine$ or sulphachlorpyridazine$ or sulphadimethoxine$ or sulphadoxine$ or sulphaguanidine$ or sulphamerazine$ or sulphameter$ or sulphamethazine$ or sulphamethoxypyridazine$).ti,ab.
96. (sulfamonomethoxine$ or sulfamoxole$ or sulfaphenazole$ or sulfapyridine$ or sulfaquinoxaline$ or sulfathiazole$ or sulfamethizole$ or sulfisomidine$ or sulfisoxazole$ or sulfasalazine$ or sumatriptan$ or xipamide$ or thioamide$ or thioacetamide$ or sulphamonomethoxine$ or sulphamoxole$ or sulphaphenazole$ or sulphapyridine$ or sulphaquinoxaline$ or sulphathiazole$ or sulphamethizole$ or sulphisomidine$ or sulphisoxazole$ or sulphasalazine$).ti,ab.
97. (tetracycline$ or demeclocycline$ or doxycycline$ or lymecycline$ or minocycline$ or oxytetracycline$).ti,ab.
98. (chlortetracycline$ or methacycline$ or rolitetracycline$).ti,ab.
99. (cloranfenicol$ or chloramphenicol$).ti,ab.
100. (thiamphenicol$ or kloramfenikol$ or levomycetin$ or chlornitromycin$ or chlorocid$ or chloromycetin$ or detreomycin$ or ophthochlor$ or syntomycin$).ti,ab.
101. (clindamycin$ or dalacin c or cleocin$ or chlo?lincocin$).ti,ab.
102. exp Metronidazole/
103. (linezolid$ or trivazol$ or vagilen$ or clont$ or danizol$ or fagyl$ or ginefavir$ or metrogel$ or metrodzhil$ or satric$ or trichazol$ or trichopol$).ti,ab.
104. (fusidate$ adj (sodium or silver)).ti,ab.
105. (antibiotic$ or antimicrobial$).ti,ab.
106. (griseofulvin or synercid or dalfopristin or quinupristin).ti,ab.
107. (granulocyte colony stimulating factor or gcsf or ozone).ti,ab.
108. or/10-61
109. or/76-107
110. 108 or 109
111. 75 and 110 and 9

This identified 72 records.

The Cochrane Database of Systematic Reviews (CDSR) and the Cochrane Controlled Trials Register (CCTR) [Searched: 12 November 2002 via the Cochrane Library (2002, Issue 4)]

#1. (neuroischemic near foot)
#2. (neuroischaemic near foot)
#3. (neuroischemic near feet)
#4. (neuroischaemic near feet)
#5. (neuroischemic near ulcer*)
#6. (neuroischaemic near ulcer*)
#7. (ischemic near foot)
#8. (ischemic near feet)
#9. (ischemic near ulcer*)
#10. (ischaemic near foot)
#11. (ischaemic near feet)
#12. (ischaemic near ulcer*)
#13. (diabetic near foot)
#14. (diabetic near feet)
#15. (diabetic near ulcer*)
#16. (neuropathic near foot)
#17. (neuropathic near feet)
#18. (neuropathic near ulcer*)
#19. (pedal near ulcer*)
#20. (pedal near septic)
#21. (pedal near wound*)
#22. (plantar near ulcer*)
#23. (plantar near septic)
#24. (plantar near wound*)
#25. (foot near ulcer*)
#26. (foot near septic)
#27. (foot near wound*)
#28. (feet near ulcer*)
#29. (feet near septic)
#30. (feet near wound*)
#31. (heel near ulcer*)
#32. (heel near septic)
#33. (heel near wound*)
#34. (foot near diabet*)
#35. (feet near diabet*)
#36. (deep next foot next infection*)
#37. (crural near ulcer*)
#38. (leg near ulcer*)
#39. (venous near leg)
#40. (venous near ulcer*)
#41. (stasis near leg)
#42. (stasis near ulcer*)
#43. (varicos* near leg)
#44. (varicos* near ulcer*)
#45. ((lower next extremit*) near ulcer*)
#46. ((lower next extremit*) near wound*)

#47. ((lower next limb*) near ulcer*)
#48. ((lower next limb*) near wound*)
#49. (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48)
#50. LEG ULCER explode all trees (MeSH)
#51. (#49 or #50)
#52. ACETIC ACID explode all trees (MeSH)
#53. ((acetic next acid*) or acetate* or acetamide* or acetoxyacetyaminofluorene* or hydrooxyacetylaminofluorene* or allylisopropylacetamide*)
#54. (idoacetamide* or idoacetate* or piracetam* or thioacetamide* or galolinium* or technetium* or dichoroacetate* or fluoroacetate* or idoacetate*)
#55. (foscarnet* or thioglycolate* or (acetic next anhydride*))
#56. (aminooxyacetic or edetic or egtazic or idoacetic or nitrilotriacetic or pentetic or peracetic or phosphonoacetic or trichloroacetic or trifluoroacetic)
#57. ((therapeutic next fungicide*) or (antifungal next agent*) or antifungal*)
#58. (benzoate* or butenafine* or chlorquinaldol* or cyclosporine or dichlorophen* or fluconazole* or flucytosine* or (glycyrrhizic next acid*) or hexetidine* or itraconazole* or monensin* or nifuratel* or pentamidine*)
#59. (co-amoxiclav* or (sodium next benzoate*) or thimerosal* or thiram* or thymol* or tolnaftate* or tomatine* or triacetin* or trimetrexate*)
#60. (amoroldine* or (benzoic next acid*) or clotrimazole* or econazole* or ketoconazole* or miconazole* or nystatin* or (salicyclic next acid*) or sulconazole* or terbinafine* or tioconazole* or undecenoate*)
#61. (antiviral* or (anti next viral*) or idoxuridine*)
#62. (acetylcysteine* or acyclovir* or amantadine* or aphidicolin* or aprotinin* or brefeldin or bromodeoxyuridine* or cytarabine* or deoxyglucose* or (dextran next sulfate*))
#63. (dideoxyadenosine* or dideoxynucleoside* or (dihematoporphyrin next ether*) or ditiocarb* or filipin* or floxuridine* or ganciclovir* or (inosine next pranobex) or (interferon next alfa*) or (interferon next type*) or (interferon next beta) or (interferon next gamma) or interferons)
#64. (methisazone* or (phosphonoacetic next acid*) or (poly next a-u) or (poly next i-c) or (pyran next copolymer*) or ribavirin* or rimantadine* or streptovaricin* or (tenuazonic next acid*) or tilorone* or trifluridine* or tunicamycin* or vidarabine*)
#65. (bacitracin* or (povidone next iodine*) or betaisodona* or (polyvinylpyrrolidone next iodine*) or betadine* or disadine* or isodine* or pvp-i or pharmadine*)
#66. (cetyltrimethylammonium or cetrimide* or cetrimonium)
#67. (chlorate* or cisplatin or (hydrochloric next acid*) or chloride* or (hypochlorous next acid*) or hypochlorite* or (perchloric next acid*) or (ruthenium next red*))
#68. (eusol or phenoxyethanol* or dextranomer* or (framycetin next sulphate*) or (mandelic next acid*) or tetrabromofluorescein* or eosin or eosine or chlortetracycline* or (chloroxylenol next solution*))
#69. (edinburgh next adj next university next adj next solution next adj2 next lime)
#70. (cyclandelate* or (vanilmandelic next acid*))
#71. hexachloroph*
#72. (triclosan* or polymyxin* or polynoxylin*)
#73. (silver near dressing*)
#74. ((gentian next violet) or (crystal next violet) or (methyl next violet) or (methylrosaniline next chloride*) or (hexamethylpararosanine next chloride*))
#75. ((potassium next permanganate*) or (permanganic next acid*) or (potassium next salt*)) 36
#76. (mupirocin* or (pseudomonic next acid*) or bactroban*)
#77. (neomycin* or fradiomycin* or neamin*)
#78. ((benzyol next peroxide*) or (benzyol next superoxide*) or (diphenylglyoxal next superoxide*) or panoxyl*)
#79. ((hydrogen next peroxide*) or hydroperoxide* or oxydol* or perhydrol* or superoxol* or (diphenylglyoxal next superoxide*) or panoxyl*)
#80. (fucithalmic* or fusidate* or fusidin* or stanicide*)
#81. (liposome* near hydrogel*)
#82. ((fusidic next acid*) or inadine* or betadine*)
#83. ((cadexomer next iodine*) or chlorhexidine* or novalsan* or sebidin* or tubulicid*)

#84. (maggot* or larva or larvae or larval)
#85. ((plant next extract*) or aromatherap* or (marigold next extract*) or (calendula next officinalis) or (tagetes next patula) or (rubia next cordifolia) or manjishtha or (withania next somnifera) or ashvagandha)
#86. (phytotherapy or cascara* or curare* or (chinese next herb*) or guaiac* or ipecac* or podophyll* or psyllium* or (senna next extract*) or tragacanth* or turpentine*)
#87. ((essential next oil*) or (plant next oil*) or (tea next tree) or lavender or chamomile or camomile or rosemary)
#88. (sucrose or (sugar next paste*) or (granulated next sugar))
#89. (propolis or honey or beebread* or (bee next bread*) or (bee next glue*))
#90. (disinfect* or antisept* or anti-sept* or antiviral* or anti-viral*)
#91. (penicillin* or amdinocillin* or amox* or ampicillin* or azlocillin*)
#92. (carbenicillin* or carfecillin* or cloxacillin* or dicloxacillin* or floxacillin* or flucloxacillin* or methicillin* or mazlocillin* or nafcillin* or oxacillin* or (penicillanic next acid*))
#93. ((penicillic next acid*) or phenoxymethylpenicillin* or piperacillin* or pivampicillin* or sulbencillin* or talampicillin* or sultamicillin* or ticarcillin* or ticercillin*)
#94. (cefaclor* or cefadroxil* or cefalexin* or cefazolin* or cefamandole* or cefixime* or cefotaxime* or cefoxitin* or cefpirome* or cefpodoxime* or cefprozil*)
#95. (cefradine* or ceftazidime* or ceftizoxime* or ceftriaxone* or cefuroxime*)
#96. (cefonicid* or cefmenoxine* or cefoperazone* or cefotiam* or cefsulodin* or cephacetrile* or cephalexin* or cephaloglycin* or cephaloridine or (cephalosporanic next acid*) or cephalothin* or cephapirin* or cephradine*)
#97. ((beta next lactam*) or aztreonam* or cilastin* or imipenem* or meropenem* or sulbactam* or tazobactam*)
#98. (caprolactam* or clavulan* or moxalactam*)
#99. (aminoglycoside* or anthracycline* or aclarubicin* or daunorubicin* or carubicin* or doxorubicin* or epirubicin* or idarubicin* or nogalamycin* or menogaril* or plicamycin*)
#100. (gentamicin* or neomycin* or netilmicin* or tobramycin*)
#101. (amphotericin* or antimycin* or candicidin* or roxithromycin* or josamycin* or leucomycin* or kitasamycin* or lucensomycin* or maytansine* or mepartricin* or miocamycin*)
#102. (natamycin* or oleandomycin* or troleandomycin* or oligomycin* or rutamycin* or sirolimus* or tacrolimus* or tylosin* or propiolactone* or spironolactone* or venturicidin* or zearalenone* or zeranol*)
#103. (azithromycin* or clarithromycin* or erythromycin* or spiramycin*)
#104. (moxifloxacin* or quinolone* or ciprofloxacin* or clinafloxacin* or fluoroquinolone* or levofloxacin* or ofloxacin*)
#105. (fleroxacin* or enoxacin* or norfloxacin* or pefloxacin* or (nalidixic next acid*) or nedocromil* or (oxolinic next acid*) or quinpirole* or quipazine* or saquinavir*)
#106. (dmso or sulfoxide* or sulphoxide* or sulfonamide* or sulphonamide* or trimethoprim* or sulfamethoxazole* or sulphamethoxazole* or co-trimoxazole* or sulfadiazine* or sulphadiazine* or sulfametopyrazine* or sulfalene* or sulphametopyrazine* or sulphalene*) 2593
#107. (benzolamide* or bumetanide* or chloramine* or chlorthalidone* or clopamide* or dichlorphenamide* or ethoxzolamide* or indapamide* or mafenide* or mefruside* or metolazone* or prodenecid* or sulfanilamide* or sulphanilamide* or furosemide* or sulfacetamide* or sulphacetamide*) 2041
#108. (sulfachlorpyridazine* or sulfadimethoxine* or sulfadoxine* or sulfaguanidine* or sulfamerazine* or sulfameter* or sulfamethazine* or sulfamethoxypyridazine* or sulphachlorpyridazine* or sulphadimethoxine* or sulphadoxine* or sulphaguanidine* or sulphamerazine* or sulphameter* or sulphamethazine* or sulphamethoxypyridazine*) 290
#109. (sulfamonomethoxine* or sulfamoxole* or sulfaphenazole* or sulfapyridine* or sulfaquinoxaline* or sulfathiazole* or sulfamethizole* or sulfisomidine* or sulfisoxazole* or sulfasalazine* or sumatriptan* or xipamide* or thioamide*) 892
#110. (thioacetamide* or sulphamonomethoxine* or sulphamoxole* or sulphaphenazole* or sulphapyridine* or sulphaquinoxaline* or sulphathiazole* or sulphamethizole* or

sulphisomidine* or sulphisoxazole* or sulphasalazine*) 222
#111. (tetracycline* or demeclocycline* or doxycycline* or lymecycline* or minocycline* or oxytetracycline*) 1988
#112. (chlortetracycline* or methacycline* or rolitetracycline*) 77
#113. (cloranfenicol* or chloramphenicol*) 402
#114. (thiamphenicol* or kloramfenikol* or levomycetin* or chlornitromycin* or chlorocid* or chloromycetin* or detreomycin* or ophthochlor* or syntomycin*) 53
#115. ((clindamycin* or (dalacin next c) or cleocin* or (chlo next lincocin*)) or chlolincocin*) 796
#116. (linezolid* or trivazol* or vagilen* or clont* or danizol* or fagyl* or ginefavir* or metrogel* or metrodzhil* or satric* or trichazol* or trichopol*) 19
#117. ((granulocyte next colony next stimulating next factor) or gcsf or ozone) 892
#118. (griseofulvin or synercid or dalfopristin or quinupristin) 139
#119. (antibiotic* or antimicrobial*)
#120. (fusidate* near sodium)
#121. (fusidate* near silver)
#122. ANTI-INFECTIVE AGENTS explode all trees (MeSH)
#123. BACITRACIN explode all trees (MeSH)
#124. CHLORIDES explode all trees (MeSH)
#125. MUPIROCIN explode all trees (MeSH)
#126. HYDROGEN PEROXIDE explode all trees (MeSH)
#127. LARVA explode all trees (MeSH)
#128. COMPLEMENTARY THERAPIES explode all trees (MeSH)
#129. PLANT OILS explode all trees (MeSH)
#130. PLANT EXTRACTS explode all trees (MeSH)
#131. SUCROSE explode all trees (MeSH)
#132. HONEY explode all trees (MeSH)
#133. aminoglycosides
#134. TRIMETHOPRIM explode all trees (MeSH)
#135. METRONIDAZOLE explode all trees (MeSH)
#136. (#52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121 or #122 or #123 or #124 or #125 or #126 or #127 or #128 or #129 or #130 or #131 or #132 or #133 or #134 or #135)
#137. #51 and #136

This identified 35 reviews in the CDSR (of which 12 were protocols) and 176 potential trials in CCTR.

EMBASE (1980–2002 week 44)
(searched: 6 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. exp clinical trial/
2. Single Blind Procedure/
3. double Blind Procedure/
4. placebo/
5. meta-analysis/
6. randomization/
7. randomized-controlled-trial/
8. controlled-study/
9. exp evidence-based-medicine/
10. exp comparative-study/
11. (clinical trial$ or random$ or placebo$ or control or controls or controlled).ti,ab.
12. (single blind$ or double blind$ or trebl$ blind$ or tripl$ blind$).ti,ab.
13. (meta-analys$ or meta analys$ or comparison group or standard treatment$ or systematic review$).ti,ab.
14. or/1-13
15. exp animal/
16. exp human/
17. nonhuman/
18. 15 not (15 and 16)
19. 17 not (17 and 16)
20. 14 not (18 or 19)
21. exp Acetic Acid/
22. (acetic acid$ or acetate$ or acetamide$ or acetoxyacetylaminofluorene$ or hydroxyacetylaminofluorene$ or allylisopropylacetamide$).ti,ab.
23. (idoacetamide$ or idoacetate$ or piracetam$ or thioacetamide$ or gadolinium$ or technetium$ or dichoroacetate$ or fluoroacetate$ or iodoacetate$).ti,ab.
24. (foscarnet$ or thioglycolate$ or acetic anhydride$).ti,ab.
25. ((aminooxyacetic or edetic or egtazic or iodoacetic or nitrilotriacetic or pentetic or peracetic or phosphonoacetic or trichloroacetic or trifluoroacetic) adj acid$).ti,ab.
26. exp ANTIFUNGAL AGENTS/

27. (therapeutic fungicide$ or antifungal agent$ or antifungals).ti,ab.
28. (benzoate$ or butenafine$ or chlorquinaldol$ or cyclosporine$ or dichlorophen$ or fluconazole$ or flucytosine$ or glycyrrhizic acid$ or hexetidine$ or itraconazole$ or monensin$ or nifuratel$ or pentamidine$).ti,ab.
29. (co-amoxiclav$ or sodium benzoate$ or thimerosal$ or thiram$ or thymol$ or tolnaftate$ or tomatine$ or triacetin$ or trimetrexate$).ti,ab.
30. (amoroldine$ or benzoic acid$ or clotrimazole$ or econazole$ or ketoconazole$ or miconazole$ or nystatin$ or Salicylic acid$ or sulconazole$ or terbinafine$ or tioconazole$ or undecenoate$).ti,ab.
31. (antiviral$ or anti viral$ or idoxuridine$).ti,ab.
32. (acetylcysteine$ or acyclovir$ or amantadine$ or aphidicolin$ or aprotinin$ or brefeldin or bromodeoxyuridine$ or cytarabine$ or deoxyglucose$ or dextran sulfate$).ti,ab.
33. (dideoxyadenosine$ or dideoxynucleoside$ or dihematoporphyrin ether$ or ditiocarb$ or filipin$ or floxuridine$ or ganciclovir$ or inosine pranobex or interferon alfa$ or interferon type$ or interferon beta or interferon gamma or interferons).ti,ab.
34. (methisazone$ or phosphonoacetic acid$ or poly a-u or poly i-c or pyran copolymer$ or ribavirin$ or rimantadine$ or streptovaricin$ or tenuazonic acid$ or tilorone$ or trifluridine$ or tunicamycin$ or vidarabine$).ti,ab.
35. exp BACITRACIN/
36. exp Povidone-Iodine/
37. (bacitracin$ or povidone iodine$ or betaisodona$ or polyvinylpyrrolidone iodine$ or betadine$ or disadine$ or isodine$ or pvp-i or pharmadine$).ti,ab.
38. exp Cetrimide/
39. (cetyltrimethylammonium or cetrimide$ or cetrimonium).ti,ab.
40. exp Chlorine Derivative/
41. (chlorate$ or cisplatin or hydrochloric acid$ or chloride$ or hypochlorous acid$ or hypochlorite$ or perchloric acid$ or ruthenium red$).ti,ab.
42. exp Eosin/
43. (eusol or phenoxyethanol$ or dextranomer$ or framycetin sulphate$ or mandelic acid$ or tetrabromofluorescein$ or eosin or eosine or chlortetracycline$ or chloroxylenol solution$).ti,ab.
44. (edinburgh adj university adj solution adj2 lime).ti,ab.
45. exp Framycetin/
46. exp Mandelic Acid derivative/
47. (cyclandelate$ or vanilmandelic acid$).ti,ab.
48. exp Hexachlorophene/
49. hexachloroph#ne$.ti,ab.
50. exp Triclosan/
51. exp Polymyxin/
52. (triclosan$ or polymyxin$ or polynoxylin$).ti,ab.
53. (silver adj2 dressing$).ti,ab.
54. exp crystal Violet/
55. (gentian violet or crystal violet or methyl violet or methylrosaniline chloride$ or hexamethylpararosanine chloride$).ti,ab.
56. exp Permanganate Potassium/
57. (potassium permanganate$ or permanganic acid$ or potassium salt$).ti,ab.
58. exp pseudomonic acid/
59. (mupirocin$ or pseudomonic acid$ or bactroban$).ti,ab.
60. exp Neomycin/
61. (neomycin$ or fradiomycin$ or neamin$).ti,ab.
62. exp Benzoyl Peroxide/
63. (benzyol peroxide$ or benzyol superoxide$ or diphenylglyoxal superoxide$ or panoxyl$).ti,ab.
64. exp Hydrogen Peroxide/
65. (hydrogen peroxide$ or hydroperoxide$ or oxydol$ or perhydrol$ or superoxol$ or diphenylglyoxal superoxide$ or panoxyl$).ti,ab.
66. (fucithalmic$ or fusidate$ or fusidin$ or stanicide$).ti,ab.
67. (liposome$ adj hydrogel$).ti,ab.
68. (fusidic acid$ or inadine$ or betadine$).ti,ab.
69. exp Chlorhexidine/
70. (cadexomer iodine$ or chlorhexidine$ or novalsan$ or sebidin$ or tubulicid$).ti,ab.
71. exp Larva/
72. (maggot$ or larva or larvae or larval).ti,ab.
73. exp alternative medicine/
74. (plant extract$ or aromatherap$ or marigold extract$ or calendula officinalis or tagetes patula or rubia cordifolia or manjishtha or withania somnifera or ashvagandha).ti,ab.
75. exp Plant Extract/
76. exp Medicinal Plant/
77. (phytotherapy or cascara$ or curare$ or chinese herb$ or guaiac$ or ipecac$ or podophyll$ or psyllium$ or senna extract$ or tragacanth$ or turpentine$).ti,ab.
78. exp essential oil/ or exp vegetable oil/
79. exp Sucrose/
80. exp HONEY/
81. (essential oil$ or plant oil$ or tea tree or

lavender or chamomile or camomile or rosemary).ti,ab.
82. (sucrose or sugar paste$ or granulated sugar).ti,ab.
83. exp Propolis/
84. (propolis or honey or beebread$ or bee bread$ or bee glue$).ti,ab.
85. exp Disinfectant Agent/
86. exp Anti-Infective Agent/
87. exp Antivirus Agent/
88. (disinfect$ or antisept$ or anti-sept$ or antiviral$ or anti-viral$).ti,ab.
89. ((neuroisch?emic or isch?emic or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).ti,ab.
90. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
91. ((foot or feet) adj6 diabet$).ti,ab.
92. deep foot infection$.ti,ab.
93. exp Foot Ulcer/
94. or/89-93
95. Leg Ulcer/
96. leg varicosis/
97. ((crural or leg) adj5 ulcer$).ti,ab.
98. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).ti,ab.
99. ((venous or stasis or leg) adj5 wound$).ti.
100. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).ti,ab.
101. or/95-100
102. 94 or 101
103. exp Penicillin Derivative/
104. (penicillin$ or amdinocillin$ or amox#cillin$ or ampicillin$ or azlocillin$).ti,ab.
105. (carbenicillin$ or carfecillin$ or cloxacillin$ or dicloxacillin$ or floxacillin$ or flucloxacillin$ or methicillin$ or mazlocillin$ or nafcillin$ or oxacillin$ or penicillanic acid$).ti,ab.
106. (penicillic acid$ or phenoxymethylpenicillin$ or piperacillin$ or pivampicillin$ or sulbencillin$ or talampicillin$ or sultamicillin$ or ticarcillin$ or ticercillin$).ti,ab.
107. exp Cephalosporin Derivative/
108. (cefaclor$ or cefadroxil$ or cefalexin$ or cefazolin$ or cefamandole$ or cefixime$ or cefotaxime$ or cefoxitin$ or cefpirome$ or cefpodoxime$ or cefprozil$).ti,ab.
109. (cefradine$ or ceftazidime$ or ceftizoxime$ or ceftriaxone$ or cefuroxime$).ti,ab.
110. (cefonicid$ or cefmenoxine$ or cefoperazone$ or cefotiam$ or cefsulodin$ or cephacetrile$ or cephalexin$ or cephaloglycin$ or cephaloridine or cephalosporanic acid$ or cephalothin$ or cephapirin$ or cephradine$).ti,ab.
111. exp Lactam/
112. (beta lactam$ or aztreonam$ or cilastin$ or imipenem$ or meropenem$ or sulbactam$ or tazobactam$).ti,ab.
113. (caprolactam$ or clavulan$ or moxalactam$).ti,ab.
114. exp Aminoglycoside/
115. (Aminoglycoside$ or anthracycline$ or aclarubicin$ or daunorubicin$ or carubicin$ or doxorubicin$ or epirubicin$ or idarubicin$ or nogalamycin$ or menogaril$ or plicamycin$).ti,ab.
116. (gentamicin$ or neomycin$ or netilmicin$ or tobramycin$).ti,ab.
117. exp Macrolide/
118. (amphotericin$ or antimycin$ or candicidin$ or roxithromycin$ or josamycin$ or leucomycin$ or kitasamycin$ or lucensomycin$ or maytansine$ or mepartricin$ or miocamycin$).ti,ab.
119. (natamycin$ or oleandomycin$ or troleandomycin$ or oligomycin$ or rutamycin$ or sirolimus$ or tacrolimus$ or tylosin$ or propiolactone$ or spironolactone$ or venturicidin$ or zearalenone$ or zeranol$).ti,ab.
120. (azithromycin$ or clarithromycin$ or erythromycin$ or spiramycin$).ti,ab.
121. exp Quinolone Derivative/
122. (moxifloxacin$ or quinolone$ or ciprofloxacin$ or clinafloxacin$ or fluoroquinolone$ or levofloxacin$ or ofloxacin$).ti,ab.
123. (fleroxacin$ or enoxacin$ or norfloxacin$ or pefloxacin$ or nalidixic acid$ or nedocromil$ or oxolinic acid$ or quinpirole$ or quipazine$ or saquinavir$).ti,ab.
124. exp Sulfonamide/
125. exp Trimethoprim/
126. (dmso or sulfoxide$ or sulphoxide$ or sulfonamide$ or sulphonamide$ or trimethoprim$ or sulfamethoxazole$ or sulphamethoxazole$ or co-trimoxazole$ or sulfadiazine$ or sulphadiazine$ or sulfametopyrazine$ or sulfalene$ or sulphametopyrazine$ or sulphalene$).ti,ab.
127. (benzolamide$ or bumetanide$ or chloramine$ or chlorthalidone$ or clopamide$ or dichlorphenamide$ or ethoxzolamide$ or indapamide$ or mafenide$ or mefruside$ or metolazone$ or prodenecid$ or sulfanilamide$ or sulphanilamide$ or furosemide$ or sulfacetamide$ or sulphacetamide$).ti,ab.
128. (sulfachlorpyridazine$ or sulfadimethoxine$ or sulfadoxine$ or sulfaguanidine$ or sulfamerazine$ or sulfameter$ or

sulfamethazine$ or sulfamethoxypyridazine$ or sulphachlorpyridazine$ or sulphadimethoxine$ or sulphadoxine$ or sulphaguanidine$ or sulphamerazine$ or sulphameter$ or sulphamethazine$ or sulphamethoxypyridazine$).ti,ab.
129. (sulfamonomethoxine$ or sulfamoxole$ or sulfaphenazole$ or sulfapyridine$ or sulfaquinoxaline$ or sulfathiazole$ or sulfamethizole$ or sulfisomidine$ or sulfisoxazole$ or sulfasalazine$ or sumatriptan$ or xipamide$ or thioamide$ or thioacetamide$ or sulphamonomethoxine$ or sulphamoxole$ or sulphaphenazole$ or sulphapyridine$ or sulphaquinoxaline$ or sulphathiazole$ or sulphamethizole$ or sulphisomidine$ or sulphisoxazole$ or sulphasalazine$).ti,ab.
130. exp Tetracycline Derivative/
131. (tetracycline$ or demeclocycline$ or doxycycline$ or lymecycline$ or minocycline$ or oxytetracycline$).ti,ab.
132. (chlortetracycline$ or methacycline$ or rolitetracycline$).ti,ab.
133. exp Chloramphenicol/
134. (cloranfenicol$ or chloramphenicol$).ti,ab.
135. (thiamphenicol$ or kloramfenikol$ or levomycetin$ or chlornitromycin$ or chlorocid$ or chloromycetin$ or detreomycin$ or ophthochlor$ or syntomycin$).ti,ab.
136. exp Clindamycin/
137. (clindamycin$ or dalacin c or cleocin$ or chlo?lincocin$).ti,ab.
138. exp Metronidazole/
139. (linezolid$ or trivazol$ or vagilen$ or clont$ or danizol$ or fagyl$ or ginefavir$ or metrogel$ or metrodzhil$ or satric$ or trichazol$ or trichopol$).ti,ab.
140. exp Fusidic Acid/
141. (granulocyte colony stimulating factor or gcsf or ozone).ti,ab.
142. (fusidate$ adj (sodium or silver)).ti,ab.
143. exp Antibiotic Agent/
144. (antibiotic$ or antimicrobial$).ti,ab.
145. (griseofulvin or synercid or dalfopristin or quinupristin).ti,ab.
146. or/103-145
147. or/21-88
148. (146 or 147) and 20 and 102

This identified 449 records.

MEDLINE (1966–2002/10 week 4) and PREMEDLINE (up to 5 November 2002) (searched: 6 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. exp Acetic Acid/
2. (acetic acid$ or acetate$ or acetamide$ or acetoxyacetylaminofluorene$ or hydroxyacetylaminofluorene$ or allylisopropylacetamide$).ti,ab.
3. (idoacetamide$ or idoacetate$ or piracetam$ or thioacetamide$ or gadolinium$ or technetium$ or dichoroacetate$ or fluoroacetate$ or iodoacetate$).ti,ab.
4. (foscarnet$ or thioglycolate$ or acetic anhydride$).ti,ab.
5. ((aminooxyacetic or edetic or egtazic or iodoacetic or nitrilotriacetic or pentetic or peracetic or phosphonoacetic or trichloroacetic or trifluoroacetic) adj acid$).ti,ab.
6. exp ANTIFUNGAL AGENTS/
7. (therapeutic fungicide$ or antifungal agent$ or antifungals).ti,ab.
8. (benzoate$ or butenafine$ or chlorquinaldol$ or cyclosporine$ or dichlorophen$ or fluconazole$ or flucytosine$ or glycyrrhizic acid$ or hexetidine$ or itraconazole$ or monensin$ or nifuratel$ or pentamidine$).ti,ab.
9. (co-amoxiclav$ or sodium benzoate$ or thimerosal$ or thiram$ or thymol$ or tolnaftate$ or tomatine$ or triacetin$ or trimetrexate$).ti,ab.
10. (amoroldine$ or benzoic acid$ or clotrimazole$ or econazole$ or ketoconazole$ or miconazole$ or nystatin$ or Salicylic acid$ or sulconazole$ or terbinafine$ or tioconazole$ or undecenoate$).ti,ab.
11. (antiviral$ or anti viral$ or idoxuridine$).ti,ab.
12. (acetylcysteine$ or acyclovir$ or amantadine$ or aphidicolin$ or aprotinin$ or brefeldin or bromodeoxyuridine$ or cytarabine$ or deoxyglucose$ or dextran sulfate$).ti,ab.
13. (dideoxyadenosine$ or dideoxynucleoside$ or dihematoporphyrin ether$ or ditiocarb$ or filipin$ or floxuridine$ or ganciclovir$ or inosine pranobex or interferon alfa$ or interferon type$ or interferon beta or interferon gamma or interferons).ti,ab.
14. (methisazone$ or phosphonoacetic acid$ or poly a-u or poly i-c or pyran copolymer$ or ribavirin$ or rimantadine$ or streptovaricin$ or tenuazonic acid$ or tilorone$ or trifluridine$ or tunicamycin$ or vidarabine$).ti,ab.
15. exp BACITRACIN/
16. exp Povidone-Iodine/
17. (bacitracin$ or povidone iodine$ or betaisodona$ or polyvinylpyrrolidone iodine$ or betadine$ or disadine$ or isodine$ or pvp-i or pharmadine$).ti,ab.

18. exp Cetrimonium Compounds/
19. (cetyltrimethylammonium or cetrimide$ or cetrimonium).ti,ab.
20. exp Chlorine Compounds/
21. (chlorate$ or cisplatin or hydrochloric acid$ or chloride$ or hypochlorous acid$ or hypochlorite$ or perchloric acid$ or ruthenium red$).ti,ab.
22. exp "Eosine Yellowish-(YS)"/
23. (eusol or phenoxyethanol$ or dextranomer$ or framycetin sulphate$ or mandelic acid$ or tetrabromofluorescein$ or eosin or eosine or chlortetracycline$ or chloroxylenol solution$).ti,ab.
24. (edinburgh adj university adj solution adj2 lime).ti,ab.
25. exp Framycetin/
26. exp Mandelic Acids/
27. (cyclandelate$ or vanilmandelic acid$).ti,ab.
28. exp Hexachlorophene/
29. hexachloroph#ne$.ti,ab.
30. exp Triclosan/
31. exp Polymyxin/
32. (triclosan$ or polymyxin$ or polynoxylin$).ti,ab.
33. (silver adj2 dressing$).ti,ab.
34. exp Gentian Violet/
35. (gentian violet or crystal violet or methyl violet or methylrosaniline chloride$ or hexamethylpararosanine chloride$).ti,ab.
36. exp Potassium Permanganate/
37. (potassium permanganate$ or permanganic acid$ or potassium salt$).ti,ab.
38. exp Mupirocin/
39. (mupirocin$ or pseudomonic acid$ or bactroban$).ti,ab.
40. exp Neomycin/
41. (neomycin$ or fradiomycin$ or neamin$).ti,ab.
42. exp Benzoyl Peroxide/
43. (benzyol peroxide$ or benzyol superoxide$ or diphenylglyoxal superoxide$ or panoxyl$).ti,ab.
44. exp Hydrogen Peroxide/
45. (hydrogen peroxide$ or hydroperoxide$ or oxydol$ or perhydrol$ or superoxol$ or diphenylglyoxal superoxide$ or panoxyl$).ti,ab.
46. (fucithalmic$ or fusidate$ or fusidin$ or stanicide$).ti,ab.
47. (liposome$ adj hydrogel$).ti,ab.
48. (fusidic acid$ or inadine$ or betadine$).ti,ab.
49. exp Chlorhexidine/
50. (cadexomer iodine$ or chlorhexidine$ or novalsan$ or sebidin$ or tubulicid$).ti,ab.
51. exp Larva/
52. (maggot$ or larva or larvae or larval).ti,ab.
53. exp Complementary Therapies/
54. (plant extract$ or aromatherap$ or marigold extract$ or calendula officinalis or tagetes patula or rubia cordifolia or manjishtha or withania somnifera or ashvagandha).ti,ab.
55. exp Plant Extracts/
56. exp Plants, Medicinal/
57. (phytotherapy or cascara$ or curare$ or chinese herb$ or guaiac$ or ipecac$ or podophyll$ or psyllium$ or senna extract$ or tragacanth$ or turpentine$).ti,ab.
58. exp oils, volatile/ or exp plant oils/
59. exp Sucrose/
60. exp HONEY/
61. (essential oil$ or plant oil$ or tea tree or lavender or chamomile or camomile or rosemary).ti,ab.
62. (sucrose or sugar paste$ or granulated sugar).ti,ab.
63. exp Propolis/
64. (propolis or honey or beebread$ or bee bread$ or bee glue$).ti,ab.
65. exp Disinfectants/
66. exp Anti-Infective Agents, Local/
67. exp Antiviral Agents/
68. (disinfect$ or antisept$ or anti-sept$ or antiviral$ or anti-viral$).ti,ab.
69. ((neuroisch?emic or isch?emic or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).ti,ab.
70. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
71. ((foot or feet) adj6 diabet$).ti,ab.
72. deep foot infection$.ti,ab.
73. exp Foot Ulcer/
74. or/69-73
75. Leg Ulcer/
76. Varicose Ulcer/
77. ((crural or leg) adj5 ulcer$).ti,ab.
78. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).ti,ab.
79. ((venous or stasis or leg) adj5 wound$).ti,ab
80. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).ti,ab.
81. or/75-80
82. 74 or 81
83. random allocation/ or randomized controlled trials/
84. exp clinical trials/
85. single-blind method/ or double-blind method/ or publication bias/ or meta-analysis/
86. comparative study/
87. (controlled clinical trial or randomized controlled trial or review).pt.
88. meta-analysis.pt.
89. random$.ti,ab.
90. ((clinical adj trial$) or control$).ti,ab.

91. ((standard adj treatment$) or compar$ or (single adj blind$) or (double adj blind$)).ti,ab.
92. (placebo$ or (systematic adj review$)).ti,ab.
93. or/83-92
94. 82 and 93
95. exp Penicillins/
96. (penicillin$ or amdinocillin$ or amox#cillin$ or ampicillin$ or azlocillin$).ti,ab.
97. (carbenicillin$ or carfecillin$ or cloxacillin$ or dicloxacillin$ or floxacillin$ or flucloxacillin$ or methicillin$ or mazlocillin$ or nafcillin$ or oxacillin$ or penicillanic acid$).ti,ab.
98. (penicillic acid$ or phenoxymethylpenicillin$ or piperacillin$ or pivampicillin$ or sulbencillin$ or talampicillin$ or sultamicillin$ or ticarcillin$ or ticercillin$).ti,ab.
99. exp Cephalosporins/
100. (cefaclor$ or cefadroxil$ or cefalexin$ or cefazolin$ or cefamandole$ or cefixime$ or cefotaxime$ or cefoxitin$ or cefpirome$ or cefpodoxime$ or cefprozil$).ti,ab.
101. (cefradine$ or ceftazidime$ or ceftizoxime$ or ceftriaxone$ or cefuroxime$).ti,ab.
102. (cefonicid$ or cefmenoxine$ or cefoperazone$ or cefotiam$ or cefsulodin$ or cephacetrile$ or cephalexin$ or cephaloglycin$ or cephaloridine or cephalosporanic acid$ or cephalothin$ or cephapirin$ or cephradine$).ti,ab.
103. exp Lactams/
104. (beta lactam$ or aztreonam$ or cilastin$ or imipenem$ or meropenem$ or sulbactam$ or tazobactam$).ti,ab.
105. (caprolactam$ or clavulan$ or moxalactam$).ti,ab.
106. exp Aminoglycosides/
107. (Aminoglycoside$ or anthracycline$ or aclarubicin$ or daunorubicin$ or carubicin$ or doxorubicin$ or epirubicin$ or idarubicin$ or nogalamycin$ or menogaril$ or plicamycin$).ti,ab.
108. (gentamicin$ or neomycin$ or netilmicin$ or tobramycin$).ti,ab.
109. exp Macrolides/
110. (amphotericin$ or antimycin$ or candicidin$ or roxithromycin$ or josamycin$ or leucomycin$ or kitasamycin$ or lucensomycin$ or maytansine$ or mepartricin$ or miocamycin$).ti,ab.
111. (natamycin$ or oleandomycin$ or troleandomycin$ or oligomycin$ or rutamycin$ or sirolimus$ or tacrolimus$ or tylosin$ or propiolactone$ or spironolactone$ or venturicidin$ or zearalenone$ or zeranol$).ti,ab.
112. (azithromycin$ or clarithromycin$ or erythromycin$ or spiramycin$).ti,ab.
113. exp Quinolones/
114. (moxifloxacin$ or quinolone$ or ciprofloxacin$ or clinafloxacin$ or fluoroquinolone$ or levofloxacin$ or ofloxacin$).ti,ab.
115. (fleroxacin$ or enoxacin$ or norfloxacin$ or pefloxacin$ or nalidixic acid$ or nedocromil$ or oxolinic acid$ or quinpirole$ or quipazine$ or saquinavir$).ti,ab.
116. exp Sulfonamides/
117. exp Trimethoprim/
118. (dmso or sulfoxide$ or sulphoxide$ or sulfonamide$ or sulphonamide$ or trimethoprim$ or sulfamethoxazole$ or sulphamethoxazole$ or co-trimoxazole$ or sulfadiazine$ or sulphadiazine$ or sulfametopyrazine$ or sulfalene$ or sulphametopyrazine$ or sulphalene$).ti,ab.
119. (benzolamide$ or bumetanide$ or chloramine$ or chlorthalidone$ or clopamide$ or dichlorphenamide$ or ethoxzolamide$ or indapamide$ or mafenide$ or mefruside$ or metolazone$ or prodenecid$ or sulfanilamide$ or sulphanilamide$ or furosemide$ or sulfacetamide$ or sulphacetamide$).ti,ab.
120. (sulfachlorpyridazine$ or sulfadimethoxine$ or sulfadoxine$ or sulfaguanidine$ or sulfamerazine$ or sulfameter$ or sulfamethazine$ or sulfamethoxypyridazine$ or sulphachlorpyridazine$ or sulphadimethoxine$ or sulphadoxine$ or sulphaguanidine$ or sulphamerazine$ or sulphameter$ or sulphamethazine$ or sulphamethoxypyridazine$).ti,ab.
121. (sulfamonomethoxine$ or sulfamoxole$ or sulfaphenazole$ or sulfapyridine$ or sulfaquinoxaline$ or sulfathiazole$ or sulfamethizole$ or sulfisomidine$ or sulfisoxazole$ or sulfasalazine$ or sumatriptan$ or xipamide$ or thioamide$ or thioacetamide$ or sulphamonomethoxine$ or sulphamoxole$ or sulphaphenazole$ or sulphapyridine$ or sulphaquinoxaline$ or sulphathiazole$ or sulphamethizole$ or sulphisomidine$ or sulphisoxazole$ or sulphasalazine$).ti,ab.
122. exp Tetracyclines/
123. (tetracycline$ or demeclocycline$ or doxycycline$ or lymecycline$ or minocycline$ or oxytetracycline$).ti,ab.
124. (chlortetracycline$ or methacycline$ or rolitetracycline$).ti,ab.
125. exp Chloramphenicol/
126. (cloranfenicol$ or chloramphenicol$).ti,ab.

127. (thiamphenicol$ or kloramfenikol$ or levomycetin$ or chlornitromycin$ or chlorocid$ or chloromycetin$ or detreomycin$ or ophthochlor$ or syntomycin$).ti,ab.
128. exp Clindamycin/
129. (clindamycin$ or dalacin c or cleocin$ or chlo?lincocin$).ti,ab.
130. exp Metronidazole/
131. (linezolid$ or trivazol$ or vagilen$ or clont$ or danizol$ or fagyl$ or ginefavir$ or metrogel$ or metrodzhil$ or satric$ or trichazol$ or trichopol$).ti,ab.
132. exp Fusidic Acid/
133. (granulocyte colony stimulating factor or gcsf or ozone).ti,ab.
134. (fusidate$ adj (sodium or silver)).ti,ab.
135. exp Antibiotics/
136. (antibiotic$ or antimicrobial$).ti,ab.
137. (griseofulvin or synercid or dalfopristin or quinupristin).ti,ab.
138. or/95-137
139. or/1-68
140. 94 and (138 or 139)

This identified 590 records.

Controlled-Trials.com (searched 27 November 2002)

(venous or stasis or varicose or leg or legs or foot or feet or heel or pedal or plantar) and (ulcers or ulceration or ulcerations or ulcer or wound or wounds or infection or infections or septic or diabetic or diabetes)

This identified 89 records

Cost-effectiveness search strategies

CRD internal administration databases

NHS Economic Evaluation Database (NHS EED) (searched 13 November 2002)

The NHS Economic Evaluation Database (NHS EED) was searched via the NHS CRD's internal administration databases. This provides a more up-to-date version of the database than the Cochrane Library or the Internet and includes additional records to those in the public database. The search strategy used was as follows:

1. (neuroisch?emic or isch?emic or diabetic or neuropathic)(3W) (foot or feet or ulcer$)
2. (pedal or plantar or foot or feet or heel)(3w)(ulcer$ or septic or wound$)
3. (foot or feet)(6w)diabet$
4. deep foot infection$
5. 1 or 2 or 3 or 4

This identified 172 records.

CD-ROM resources

EconLit (1969–2002 October) (searched: 12 November 2002 on ARC SilverPlatter)

No economic filter was necessary for this database.

1. (neuroisch?emic or isch?emic or diabetic or neuropathic) near3 (foot or feet or ulcer*)
2. (pedal or plantar or foot or feet or heel) near3 (ulcer* or septic or wound*)
3. (foot or feet) near6 diabet*
4. deep foot infection*
5. 1 or 2 or 3 or 4

This identified three records.

Health Economic Evaluation Database (HEED) (Issue: November 2002) (searched: 13 November 2002 on stand-alone CD-ROM)

(neuroischemic or ischemic or neuroischaemic or ischaemic or diabetic or neuropathic) and (foot or feet or ulcer*) OR
(pedal or plantar or foot or feet or heel) and (ulcer* or septic or wound*) OR
(foot or feet) and diabet* OR
'deep foot infection' within 2 OR
'deep foot infections' within 2

This identified 77 records.

Internet databases

(Allied and Complementary Medicine) AMED (1985–2002 November) (searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. ((neuroisch?emi$ or isch?emi$ or neuropathic or diabetic) adj3 (foot or feet or ulcer$)).ti,ab.
2. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
3. ((foot or feet) adj6 diabet$).ti,ab.
4. deep foot infection$.ti,ab.
5. exp Foot Ulcer/
6. or/1-5
7. (cost or costs or costing or costed or costly).ti,ab.
8. (economic$ or pharmacoeconomic$ or price or prices or pricing).ti,ab.
9. decision making/
10. decision analysis.ti,ab.
11. decision model$.ti,ab.
12. mathematical model$.ti,ab.
13. statistical model$.ti,ab.
14. markov.ti,ab.

15. economics/ or "costs and cost analysis"/ or cost benefit analysis/ or cost of illness/
16. or/7-15
17. 6 and 16

This identified 15 records.

British Nursing Index (BNI) (1994–2002 August) (searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. ((neuroisch?emi$ or isch?emi$ or neuropathic or diabetic) adj3 (foot or feet or ulcer$)).mp.
2. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).mp.
3. ((foot or feet) adj6 diabet$).mp.
4. deep foot infection$.mp.
5. exp Foot Ulcer/
6. or/1-5
7. exp health economics/
8. (cost or costs or costed or costly or costing).mp.
9. (economic$ or pharmacoeconomic$ or price$ or pricing).mp.
10. exp decision making process/
11. markov.mp.
12. decision analysis.mp.
13. decision model$.mp.
14. mathematical model$.mp.
15. statistical model$.mp.
16. or/7-15
17. 6 and 16

This identified 23 records.

CINAHL (1982–2002 October, week 4) (searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. exp "Costs and Cost Analysis"/
2. economics.sh.
3. exp "costs and cost analysis"/
4. economic aspects of illness.sh.
5. economics, pharmaceutical.sh.
6. economic value of life.sh.
7. exp "fees and charges"/
8. budgets.sh.
9. (cost or costs or costed or costly or costing).ab,ti,hw.
10. (economic$ or pharmacoeconomic$ or price$ or pricing).ab,ti,hw.
11. or/1-10
12. markov.ti,ab.
13. Decision Making, Clinical/
14. decision analysis.ti,ab.
15. decision model$.ti,ab.
16. mathematical model$.ti,ab.
17. Models, Statistical/
18. or/12-17
19. ((neuroisch?emi$ or isch?emi$ or neuropathic or diabetic) adj3 (foot or feet or ulcer$)).ti,ab.
20. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
21. ((foot or feet) adj6 diabet$).ti,ab.
22. deep foot infection$.ti,ab.
23. exp Foot Ulcer/
24. or/19-23
25. 11 or 18
26. 24 and 25

This identified 85 records.

EMBASE (1980–2002 week 44) (searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. markov.ti,ab,hw.
2. decision analysis.ti,ab.
3. decision model$.ti,ab.
4. mathematical model$.ti,ab.
5. exp Medical Decision Making/
6. mathematical model/ or statistical model/ or stochastic model/
7. or/1-6
8. exp health economics/
9. cost/
10. exp health care cost/
11. exp economic evaluation/
12. (cost or costs or costing or costed or costly).ti,ab.
13. (economic$ or pharmacoeconomic$ or price or prices or pricing).ti,ab.
14. or/8-13
15. exp animal/
16. exp human/
17. nonhuman/
18. 15 not (15 and 16)
19. 17 not (17 and 16)
20. 14 not (18 or 19)
21. ((neuroisch?emi$ or isch?emi$ or neuropathic or diabetic) adj3 (foot or feet or ulcer$)).ti,ab.
22. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
23. ((foot or feet) adj6 diabet$).ti,ab.
24. deep foot infection$.ti,ab.
25. exp Foot Ulcer/
26. or/21-25
27. 7 or 20
28. 26 and 27

This identified 250 records.

MEDLINE (1966–2002 October. week 5) and PREMEDLINE (up to 11 November 2002) (searched: 12 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. economics/

2. exp "costs and cost analysis"/
3. economic value of life/
4. exp economics,hospital/
5. economics, medical/
6. economics, nursing/
7. economics, pharmaceutical/
8. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
9. (expenditure$ not energy).ti,ab.
10. (value adj2 money).ti,ab.
11. (budget$ or (quality adj adjusted) or qaly$).ti,ab.
12. or/1-11
13. ((metabolic adj cost$) or (energy adj cost$) or (oxygen adj cost$)).ti,ab.
14. letter.pt.
15. editorial.pt.
16. historical article.pt.
17. animal/
18. human/
19. 17 not (17 and 18)
20. (or/13-16) or 19
21. 12 not 20
22. exp decision support techniques/
23. markov.ti,ab,hw.
24. exp models, economic/
25. decision analysis.ti,ab.
26. decision model$.ti,ab.
27. mathematical model$.ti,ab.
28. or/22-27
29. ((neuroisch?emi$ or isch?emi$ or neuropathic or diabetic) adj3 (foot or feet or ulcer$)).ti,ab.
30. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
31. ((foot or feet) adj6 diabet$).ti,ab.
32. deep foot infection$.ti,ab.
33. exp Foot Ulcer/
34. or/29-33
35. 21 or 28
36. 34 and 35

This identified 261 records.

Diagnostic searches

Internet databases

(Allied And Complementary Medicine) AMED (1985–2002 November) (searched: 23 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. (specificit$ or sensitivit$).ti,ab.
2. (false negative$ or false positive$ or true negative$ or true positive$).ti,ab.
3. (positive rate$ or negative rate$).ti,ab.
4. screening.ti,ab.
5. accuracy.ti,ab.
6. reference value$.ti,ab.
7. likelihood ratio$.ti,ab.
8. (sroc or srocs or roc or rocs).ti,ab.
9. receiver operat$ curve$.ti,ab.
10. receiver operat$ character$.ti,ab.
11. diagnosis/ or diagnosis differential/ or diagnostic errors/ or exp "diagnostic techniques and procedures"/
12. (diagnos$ adj3 (efficac$ or efficien$ or effectiv$ or accura$ or correct$ or reliable or reliability)).ti,ab.
13. (diagnos$ adj3 (error$ or mistake$ or inaccura$ or incorrect or unreliable)).ti,ab.
14. diagnostic yield$.mp. or misdiagnos$.ti,ab. [mp=abstract, heading words, title]
15. (reproductivity or logistical regression).mp. or logistical model$.ti,ab. [mp=abstract, heading words, title]
16. (ability adj2 predict$).ti,ab.
17. ((test or tests or testing or standard) adj3 (reliable or reliability or performance)).ti,ab.
18. (predictive adj (value$ or standard$ or model$ or factor$)).ti,ab.
19. ((reference or index) adj (test or tests or testing)).ti,ab.
20. ((clinical or patient) adj (exam$ or asses$ or recognition or identif$ or inspection)).ti,ab.
21. (specimen$ or swab$ or smear$).ti,ab.
22. ((tissue or fluid$ or wound$ or cell or cells) adj2 sample$).ti,ab.
23. (sausage toe or dactylitis).ti,ab.
24. (puncture or biopsy or biopsies or needle aspiration$ or (bone adj2 prob$)).ti,ab.
25. exp Specimen Handling/
26. exp Microbiology/
27. (excis$ or curettage or curetage or curet or curette or aspirate or yeast or gram stain or gas liquid chromatography).ti,ab.
28. Irrigation/ or exp chromatography/ or yeasts/
29. (irrigation or lavage).ti,ab.
30. (fluorescen$ adj2 (analys$ or imag$ or antibod$ or microscopy or probe or probes or tag or tags or marker$ or technique$)).ti,ab.
31. Dyes/
32. (fluorogenic substrate$ or fluorochrome$ or immunofluorescence or ryb or red or yellow or black).ti,ab.
33. (colo?r$ adj2 (asess$ or code or codes or coding$ or concept or concepts or estimat$ or classifi$ or system$ or three)).ti,ab.
34. pseudomonas fluorescen$.ti,ab.
35. ((Fluorescen$ or vital) adj5 dye$).ti,ab.
36. (electronic adj (sensor$ or nose)).ti,ab.
37. (e-nose or e-sensor$ or x-ray$ or mri or nmror (gallium adj2 citrate)).ti,ab.
38. exp diagnosic imaging/

39. (imaging or scanning or scan or (computed and tomograph$) or ct or cat or (technetium adj3 bone) or indium 111 or (labelled and white and cell) or hmpo or scintigraph$ or (magnetic and resonance) or (nuclear and magnetic)).ti,ab.
40. (tissue adj (culture$ or diagnos$ or antigen$)).ti,ab.
41. microscopy/
42. (aerob$ or anaerob$).ti,ab.
43. (biological or mycobacter$ or coloni$ or contaminat$ or bacter$ or antimicrob$ or anti-microb$ or microb$ or osteomyeliti$ or celluliti$ or infect$).ti,ab.
44. exp BACTERIA/
45. (gram adj (negative or positive)).ti,ab.
46. (plate culture$ or colony count$).ti,ab.
47. (pus or cicatrix or exudate or suppuration or oozing or discharge or drainage or odo?r or malodo?r or erythema or redness or warmth or tender$ or pain$ or induration or fluctuance or swelling or swollen or warm or heat).ti,ab.
48. (signs and symptoms).mp.
49. abscess/ or Cicatrix/ or Drainage/ or Erythema/ or smell/ or inflammation/
50. pain/ or exp neuralgia/ or pain intractable/
51. (public health laboratory or phl).ti,ab.
52. (molecular adj (screen$ or diagnos$)).ti,ab.
53. (polymerase chain reaction adj3 screening).ti,ab.
54. exp polymerase chain reaction/
55. (primed adj2 situ label$).ti,ab.
56. random amplified polymorphic dna.ti,ab.
57. reverse transcriptase pcr.ti,ab.
58. (pcr or ctpcr or mlst).ti,ab.
59. multi locus sequence typing.ti,ab.
60. 16 s rdna.ti,ab.
61. (fluoresce$ adj4 diagnos$).ti,ab.
62. ((near patient or site or onsite or rapid) adj (test$ or system$ or assessment$ or diagnos$ or analysis)).ti,ab.
63. (point adj2 care adj (test$ or system$ or assessment$ or diagnos$ or analysis)).ti,ab.
64. ((neuroisch?emi$ or isch?emi$ or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).ti,ab.
65. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
66. ((foot or feet) adj6 diabet$).ti,ab.
67. deep foot infection$.ti,ab.
68. exp Foot Ulcer/
69. or/64-68
70. Leg Ulcer/
71. Varicose Ulcer/
72. ((crural or leg) adj5 ulcer$).ti,ab.
73. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).ti,ab.
74. ((venous or stasis or leg) adj5 wound$).ti.
75. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).ti,ab.
76. or/70-75
77. 69 or 76
78. or/1-19
79. or/20-63
80. 77 and 78 and 79

This identified 44 records.

British Nursing Index (BNI) (1994–2002 September) (searched: 23 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. (specificit$ or sensitivit$).mp.
2. (false negative$ or false positive$ or true negative$ or true positive$).mp.
3. (positive rate$ or negative rate$).mp.
4. screening.mp.
5. accuracy.mp.
6. reference value$.mp.
7. likelihood ratio$.mp.
8. (sroc or srocs or roc or rocs).mp.
9. receiver operat$ curve$.mp.
10. receiver operat$ character$.mp.
11. exp diagnosis/
12. (diagnos$ or misdiagnos$).mp.
13. (reproductivity or logistical regression or logistical model$).mp.
14. (ability adj2 predict$).mp.
15. ((test or tests or testing or standard) adj3 (reliable or reliability or performance)).mp.
16. (predictive adj (value$ or standard$ or model$ or factor$)).mp.
17. ((reference or index) adj (test or tests or testing)).mp.
18. ((clinical or patient) adj (exam$ or asses$ or recognition or identif$ or inspection)).mp.
19. (specimen$ or swab$ or smear$).mp.
20. ((tissue or fluid$ or wound$ or cell or cells) adj2 sample$).mp.
21. (sausage toe or dactylitis).mp.
22. (puncture or biopsy or biopsies or needle aspiration$ or (bone adj2 prob$)).mp.
23. exp Microbiology/
24. (excis$ or curettage or curetage or curet or curette or aspirate or yeast or gram stain or gas liquid chromatography).mp.
25. (irrigation or lavage).mp.
26. (fluorescen$ adj2 (analys$ or imag$ or antibod$ or microscopy or probe or probes or tag or tags or marker$ or technique$)).mp.
27. (fluorogenic substrate$ or fluorochrome$ or immunofluorescence or ryb or red or yellow or black).mp.
28. (colo?r$ adj2 (asess$ or code or codes or

coding$ or concept or concepts or estimat$ or classifi$ or system$ or three)).mp.
29. pseudomonas fluorescen$.mp.
30. ((Fluorescen$ or vital) adj5 dye$).mp.
31. (electronic adj (sensor$ or nose)).mp.
32. (e-nose or e-sensor$ or x-ray$ or mri or nmr or (gallium adj2 citrate)).mp.
33. exp imaging/
34. (imaging or scanning or scan or (computed and tomograph$) or ct or cat or (technetium adj3 bone) or indium 111 or (labelled and white and cell) or hmpo or scintigraph$ or (magnetic and resonance) or (nuclear and magnetic)).mp.
35. (tissue adj (culture$ or diagnos$ or antigen$)).mp.
36. (aerob$ or anaerob$).mp.
37. (biological or mycobacter$ or coloni$ or contaminat$ or bacter$ or antimicrob$ or anti-microb$ or microb$ or osteomyeliti$ or celluliti$ or infect$).mp.
38. exp BACTERIA/
39. (gram adj (negative or positive)).mp.
40. (plate culture$ or colony count$).mp.
41. (pus or cicatrix or exudate or suppuration or oozing or discharge or drainage or odo?r or malodo?r or erythema or redness or warmth or tender$ or pain$ or induration or fluctuance or swelling or swollen or warm or heat).mp.
42. (signs and symptoms).mp.
43. (public health laboratory or phl).mp.
44. (molecular adj (screen$ or diagnos$)).mp.
45. (polymerase chain reaction adj3 screening).mp.
46. (primed adj2 situ label$).mp.
47. random amplified polymorphic dna.mp.
48. reverse transcriptase pcr.mp.
49. (pcr or ctpcr or mlst).mp.
50. multi locus sequence typing.mp.
51. 16 s rdna.mp.
52. (fluoresce$ adj4 diagnos$).mp.
53. ((near patient or site or onsite or rapid) adj (test$ or system$ or assessment$ or diagnos$ or analysis)).mp.
54. (point adj2 care adj (test$ or system$ or assessment$ or diagnos$ or analysis)).mp.
55. ((neuroisch?emi$ or isch?emi$ or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).mp.
56. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).mp.
57. ((foot or feet) adj6 diabet$).mp.
58. deep foot infection$.mp.
59. Leg Ulcer/
60. ((crural or leg) adj5 ulcer$).mp.
61. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).mp.
62. ((venous or stasis or leg) adj5 wound$).mp.
63. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).mp.
64. or/55-63
65. or/1-17
66. or/18-54
67. 64 and 65 and 66

This identified 54 records.

CINAHL (1982–2002 week 4) (searched: 23 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. exp "Sensitivity and Specificity"/
2. False Positive Reactions/
3. False Negative Reactions/
4. (specificit$ or sensitivit$).ti,ab.
5. (false negative$ or false positive$ or true negative$ or true positive$).ti,ab.
6. (positive rate$ or negative rate$).ti,ab.
7. screening.ti,ab.
8. accuracy.ti,ab.
9. reference value$.ti,ab.
10. likelihood ratio$.ti,ab.
11. (sroc or srocs or roc or rocs).ti,ab.
12. receiver operat$ curve$.ti,ab.
13. receiver operat$ character$.ti,ab.
14. exp Logistic Regression/
15. diagnosis/ or diagnosis, delayed/ or diagnosis, differential/ or diagnosis, laboratory/ or diagnostic errors/ or diagnostic tests, routine/ or predictive value of tests/
16. (diagnos$ adj3 (efficac$ or efficien$ or effectiv$ or accura$ or correct$ or reliable or reliability)).ti,ab.
17. (diagnos$ adj3 (error$ or mistake$ or inaccura$ or incorrect or unreliable)).ti,ab.
18. diagnostic yield$.mp. or misdiagnos$.ti,ab. [mp=title, cinahl subject heading, abstract, instrumentation]
19. (reproductivity or logistical regression).mp. or logistical model$.ti,ab. [mp=title, cinahl subject heading, abstract, instrumentation]
20. (ability adj2 predict$).ti,ab.
21. ((test or tests or testing or standard) adj3 (reliable or reliability or performance)).ti,ab.
22. (predictive adj (value$ or standard$ or model$ or factor$)).ti,ab.
23. ((reference or index) adj (test or tests or testing)).ti,ab.
24. ((clinical or patient) adj (exam$ or asses$ or recognition or identif$ or inspection)).ti,ab.
25. (specimen$ or swab$ or smear$).ti,ab.
26. ((tissue or fluid$ or wound$ or cell or cells) adj2 sample$).ti,ab.
27. (sausage toe or dactylitis).ti,ab.

28. (puncture or biopsy or biopsies or needle aspiration$ or (bone adj2 prob$)).ti,ab.
29. exp Specimen Handling/
30. exp Biopsy/
31. exp Microbiological Techniques/
32. Curettage/
33. (excis$ or curettage or curetage or curet or curette or aspirate or yeast or gram stain or gas liquid chromatography).ti,ab.
34. exp Irrigation/ or exp chromatography/ or yeasts/
35. (irrigation or lavage).ti,ab.
36. (fluorescen$ adj2 (analys$ or imag$ or antibod$ or microscopy or probe or probes or tag or tags or marker$ or technique$)).ti,ab.
37. exp Fluorescent Antibody Technique/
38. exp Fluorescent Dyes/
39. (fluorogenic substrate$ or fluorochrome$ or immunofluorescence or ryb or red or yellow or black).ti,ab.
40. (colo?r$ adj2 (asess$ or code or codes or coding$ or concept or concepts or estimat$ or classifi$ or system$ or three)).ti,ab.
41. pseudomonas fluorescen$.ti,ab.
42. ((Fluorescen$ or vital) adj5 dye$).ti,ab.
43. (electronic adj (sensor$ or nose)).ti,ab.
44. (e-nose or e-sensor$ or x-ray$ or mri or nmr or (gallium adj2 citrate)).ti,ab.
45. exp diagnostic imaging/
46. (imaging or scanning or scan or (computed and tomograph$) or ct or cat or (technetium adj3 bone) or indium 111 or (labelled and white and cell) or hmpo or scintigraph$ or (magnetic and resonance) or (nuclear and magnetic)).ti,ab.
47. (tissue adj (culture$ or diagnos$ or antigen$)).ti,ab.
48. exp Tissue Culture/ or exp microscopy/
49. (aerob$ or anaerob$).ti,ab.
50. (biological or mycobacter$ or coloni$ or contaminat$ or bacter$ or antimicrob$ or anti-microb$ or microb$ or osteomyeliti$ or celluliti$ or infect$).ti,ab.
51. exp BACTERIA/
52. (gram adj (negative or positive)).ti,ab.
53. (plate culture$ or colony count$).ti,ab.
54. (pus or cicatrix or exudate or suppuration or oozing or discharge or drainage or odo?r or malodo?r or erythema or redness or warmth or tender$ or pain$ or induration or fluctuance or swelling or swollen or warm or heat).ti,ab.
55. (signs and symptoms).mp.
56. abscess/ or cellulitis/ or exp Cicatrix/ or Drainage/ or exp Erythema/ or Odors/
57. pain/ or neuralgia/ or "exudates and transudates"/
58. (public health laboratory or phl).ti,ab.
59. (molecular adj (screen$ or diagnos$)).ti,ab.
60. (polymerase chain reaction adj3 screening).ti,ab.
61. exp polymerase chain reaction/
62. (primed adj2 situ label$).ti,ab.
63. random amplified polymorphic dna.ti,ab.
64. reverse transcriptase pcr.ti,ab.
65. (pcr or ctpcr or mlst).ti,ab.
66. multi locus sequence typing.ti,ab.
67. 16 s rdna.ti,ab.
68. (fluoresce$ adj4 diagnos$).ti,ab.
69. ((near patient or site or onsite or rapid) adj (test$ or system$ or assessment$ or diagnos$ or analysis)).ti,ab.
70. (point adj2 care adj (test$ or system$ or assessment$ or diagnos$ or analysis)).ti,ab.
71. ((neuroisch?emi$ or isch?emi$ or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).ti,ab.
72. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
73. ((foot or feet) adj6 diabet$).ti,ab.
74. deep foot infection$.ti,ab.
75. exp Foot Ulcer/
76. or/71-75
77. Leg Ulcer/
78. Varicose Ulcer/
79. ((crural or leg) adj5 ulcer$).ti,ab.
80. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).ti,ab.
81. ((venous or stasis or leg) adj5 wound$).ti.
82. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).ti,ab.
83. or/77-82
84. 76 or 83
85. or/1-23
86. or/24-70
87. 84 and 85 and 86

This identified 68 records.

EMBASE (1980–2002 week 46) (searched: 24 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. "Sensitivity and Specificity"/
2. (specificit$ or sensitivit$).ti,ab.
3. (false negative$ or false positive$ or true negative$ or true positive$).ti,ab.
4. (positive rate$ or negative rate$).ti,ab.
5. screening.ti,ab.
6. accuracy.ti,ab.
7. reference value$.ti,ab.
8. likelihood ratio$.ti,ab.
9. (sroc or srocs or roc or rocs).ti,ab.
10. receiver operat$ curve$.ti,ab.
11. receiver operat$ character$.ti,ab.
12. receiver operating characteristic/ or roc curve/

13. logistic regression analysis/
14. diagnos$.ti,ab,hw.
15. exp diagnosis/
16. misdiagnos$.ti,ab.
17. (reproductivity or logistical regression).mp. or logistical model$.ti,ab. [mp=abstract, heading words, title]
18. (ability adj2 predict$).ti,ab.
19. ((test or tests or testing or standard) adj3 (reliable or reliability or performance)).ti,ab.
20. (predictive adj (value$ or standard$ or model$ or factor$)).ti,ab.
21. ((reference or index) adj (test or tests or testing)).ti,ab.
22. ((clinical or patient) adj (exam$ or asses$ or recognition or identif$ or inspection)).ti,ab.
23. (specimen$ or swab$ or smear$).ti,ab.
24. ((tissue or fluid$ or wound$ or cell or cells) adj2 sample$).ti,ab.
25. (sausage toe or dactylitis).ti,ab.
26. (puncture or biopsy or biopsies or needle aspiration$ or (bone adj2 prob$)).ti,ab.
27. biopsy/ or bone biopsy/ or exp biopsy technique/
28. exp microbiological examination/ or exp "microbiological phenomena and functions"/
29. Curettage/
30. (excis$ or curettage or curetage or curet or curette or aspirate or yeast or gram stain or gas liquid chromatography).ti,ab.
31. wound irrigation/ or gas liquid chromatography/ or yeast/
32. (irrigation or lavage).ti,ab.
33. (fluorescen$ adj2 (analys$ or imag$ or antibod$ or microscopy or probe or probes or tag or tags or marker$ or technique$)).ti,ab.
34. Fluorescent Antibody Technique/
35. exp Fluorescent Dye/
36. (fluorogenic substrate$ or fluorochrome$ or immunofluorescence or ryb or red or yellow or black).ti,ab.
37. (colo?r$ adj2 (asess$ or code or codes or coding$ or concept or concepts or estimat$ or classifi$ or system$ or three)).ti,ab.
38. Pseudomonas fluorescens/
39. pseudomonas fluorescen$.ti,ab.
40. ((Fluorescen$ or vital) adj5 dye$).ti,ab.
41. (electronic adj (sensor$ or nose)).ti,ab.
42. (e-nose or e-sensor$ or x-ray$ or mri or nmr or (gallium adj2 citrate)).ti,ab.
43. tomography/ or exp computer assisted tomography/ or nuclear magnetic resonance imaging/ or exp X-Ray/
44. (imaging or scanning or scan or (computed and tomograph$) or ct or cat or (technetium adj3 bone) or indium 111 or (labelled and white and cell) or hmpo or scintigraph$ or (magnetic and resonance) or (nuclear and magnetic)).ti,ab.
45. (tissue adj (culture$ or diagnos$ or antigen$)).ti,ab.
46. exp Tissue Culture/ or exp microscopy/
47. (aerob$ or anaerob$).ti,ab.
48. (biological or mycobacter$ or coloni$ or contaminat$ or bacter$ or antimicrob$ or anti-microb$ or microb$ or osteomyeliti$ or celluliti$ or infect$).ti,ab.
49. exp BACTERIA/
50. (gram adj (negative or positive)).ti,ab.
51. (plate culture$ or colony count$).ti,ab.
52. (pus or cicatrix or exudate or suppuration or oozing or discharge or drainage or odo?r or malodo?r or erythema or redness or warmth or tender$ or pain$ or induration or fluctuance or swelling or swollen or warm or heat).ti,ab.
53. (signs and symptoms).mp.
54. abscess/ or cellulitis/ or abscess drainage/ or wound drainage/ or exp Erythema/ or Odor/
55. pain/ or exp bone pain/ or exp leg pain/ or exp neuralgia/ or exp exudate/ or cyst fluid/
56. (public health laboratory or phl).ti,ab.
57. (molecular adj (screen$ or diagnos$)).ti,ab.
58. (polymerase chain reaction adj3 screening).ti,ab.
59. exp polymerase chain reaction/
60. (primed adj2 situ label$).ti,ab.
61. random amplified polymorphic dna.ti,ab.
62. reverse transcriptase pcr.ti,ab.
63. (pcr or ctpcr or mlst).ti,ab.
64. multi locus sequence typing.ti,ab.
65. 16 s rdna.ti,ab.
66. (fluoresce$ adj4 diagnos$).ti,ab.
67. ((near patient or site or onsite or rapid) adj (test$ or system$ or assessment$ or diagnos$ or analysis)).ti,ab.
68. (point adj2 care adj (test$ or system$ or assessment$ or diagnos$ or analysis)).ti,ab.
69. ((neuroisch?emi$ or isch?emi$ or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).ti,ab.
70. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
71. ((foot or feet) adj6 diabet$).ti,ab.
72. deep foot infection$.ti,ab.
73. exp Foot Ulcer/
74. or/69-73
75. Leg Ulcer/
76. leg varicosis/
77. ((crural or leg) adj5 ulcer$).ti,ab.
78. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).ti,ab.
79. ((venous or stasis or leg) adj5 wound$).ti.
80. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).ti,ab.

81. or/75-80
82. 74 or 81
83. or/1-21
84. or/22-68
85. 82 and 83 and 84
86. exp diagnosis/
87. diagnos$.mp.
88. 86 or 87 or 83
89. 88 and 82 and 84

This identified 1549 records.

MEDLINE (1996–2002 October, week 5) and PREMEDLINE (up to 21 November 2002) (searched: 24 November 2002 on OvidWeb Gateway at http://gateway.ovid.com/athens)

1. exp "Sensitivity and Specificity"/
2. False Positive Reactions/
3. False Negative Reactions/
4. (specificit$ or sensitivit$).ti,ab.
5. (false negative$ or false positive$ or true negative$ or true positive$).ti,ab.
6. (positive rate$ or negative rate$).ti,ab.
7. screening.ti,ab.
8. accuracy.ti,ab.
9. reference value$.ti,ab.
10. likelihood ratio$.ti,ab.
11. (sroc or srocs or roc or rocs).ti,ab.
12. receiver operat$ curve$.ti,ab.
13. receiver operat$ character$.ti,ab.
14. roc-curve/ or logistic-models/ or likelihood-functions/
15. diagnosis/ or exp "diagnostic errors"/ or exp "diagnostic techniques and procedures"/ or exp "laboratory techniques and procedures"/
16. (diagnos$ adj3 (efficac$ or efficien$ or effectiv$ or accura$ or correct$ or reliable or reliability)).ti,ab.
17. (diagnos$ adj3 (error$ or mistake$ or inaccura$ or incorrect or unreliable)).ti,ab.
18. diagnostic yield$.mp. or misdiagnos$.ti,ab. [mp=ti, ab, rw, sh]
19. (reproductivity or logistical regression).mp. or logistical model$.ti,ab. [mp=ti, ab, rw, sh]
20. (ability adj2 predict$).ti,ab.
21. ((test or tests or testing or standard) adj3 (reliable or reliability or performance)).ti,ab.
22. (predictive adj (value$ or standard$ or model$ or factor$)).ti,ab.
23. ((reference or index) adj (test or tests or testing)).ti,ab.
24. ((clinical or patient) adj (exam$ or asses$ or recognition or identif$ or inspection)).ti,ab.
25. (specimen$ or swab$ or smear$).ti,ab.
26. ((tissue or fluid$ or wound$ or cell or cells) adj2 sample$).ti,ab.
27. (sausage toe or dactylitis).ti,ab.
28. (puncture or biopsy or biopsies or needle aspiration$ or (bone adj2 prob$)).ti,ab.
29. exp Specimen Handling/
30. exp Biopsy/
31. exp Microbiological Techniques/
32. Curettage/
33. (excis$ or curettage or curetage or curet or curette or aspirate or yeast or gram stain or gas liquid chromatography).ti,ab.
34. exp Irrigation/ or exp chromatography/ or yeasts/
35. (irrigation or lavage).ti,ab.
36. (fluorescen$ adj2 (analys$ or imag$ or antibod$ or microscopy or probe or probes or tag or tags or marker$ or technique$)).ti,ab.
37. exp Fluorescent Antibody Technique/
38. exp Fluorescent Dyes/
39. (fluorogenic substrate$ or fluorochrome$ or immunofluorescence or ryb or red or yellow or black).ti,ab.
40. (colo?r$ adj2 (asess$ or code or codes or coding$ or concept or concepts or estimat$ or classifi$ or system$ or three)).ti,ab.
41. exp Pseudomonas fluorescens/
42. pseudomonas fluorescen$.ti,ab.
43. ((Fluorescen$ or vital) adj5 dye$).ti,ab.
44. (electronic adj (sensor$ or nose)).ti,ab.
45. (e-nose or e-sensor$ or x-ray$ or mri or nmr or (gallium adj2 citrate)).ti,ab.
46. exp Tomography, X-Ray Computed/ or exp Magnetic Resonance Imaging/ or exp X-Rays/
47. (imaging or scanning or scan or (computed and tomograph$) or ct or cat or (technetium adj3 bone) or indium 111 or (labelled and white and cell) or hmpo or scintigraph$ or (magnetic and resonance) or (nuclear and magnetic)).ti,ab.
48. (tissue adj (culture$ or diagnos$ or antigen$)).ti,ab.
49. exp Tissue Culture/ or exp microscopy/
50. (aerob$ or anaerob$).ti,ab.
51. (biological or mycobacter$ or coloni$ or contaminat$ or bacter$ or antimicrob$ or anti-microb$ or microb$ or osteomyeliti$ or celluliti$ or infect$).ti,ab.
52. exp BACTERIA/
53. (gram adj (negative or positive)).ti,ab.
54. (plate culture$ or colony count$).ti,ab.
55. (pus or cicatrix or exudate or suppuration or oozing or discharge or drainage or odo?r or malodo?r or erythema or redness or warmth or tender$ or pain$ or induration or fluctuance or swelling or swollen or warm or heat).ti,ab.
56. (signs and symptoms).mp.
57. suppuration/ or abscess/ or cellulitis/ or Cicatrix/ or Drainage/ or Erythema/ or Odors/

58. pain/ or neuralgia/ or pain, intractable/ or "exudates and transudates"/ or cyst fluid/
59. (public health laboratory or phl).ti,ab.
60. (molecular adj (screen$ or diagnos$)).ti,ab.
61. (polymerase chain reaction adj3 screening).ti,ab.
62. exp polymerase chain reaction/
63. (primed adj2 situ label$).ti,ab.
64. random amplified polymorphic dna.ti,ab.
65. reverse transcriptase pcr.ti,ab.
66. (pcr or ctpcr or mlst).ti,ab.
67. multi locus sequence typing.ti,ab.
68. 16 s rdna.ti,ab.
69. (fluoresce$ adj4 diagnos$).ti,ab.
70. ((near patient or site or onsite or rapid) adj (test$ or system$ or assessment$ or diagnos$ or analysis)).ti,ab.
71. (point adj2 care adj (test$ or system$ or assessment$ or diagnos$ or analysis)).ti,ab.
72. ((neuroisch?emi$ or isch?emi$ or diabetic or neuropathic) adj3 (foot or feet or ulcer$)).ti,ab.
73. ((pedal or plantar or foot or feet or heel) adj3 (ulcer$ or septic or wound$)).ti,ab.
74. ((foot or feet) adj6 diabet$).ti,ab.
75. deep foot infection$.ti,ab.
76. exp Foot Ulcer/
77. or/72-76
78. Leg Ulcer/
79. Varicose Ulcer/
80. ((crural or leg) adj5 ulcer$).ti,ab.
81. ((venous or stasis or varicos$) adj5 (leg or ulcer$)).ti,ab.
82. ((venous or stasis or leg) adj5 wound$).ti,ab.
83. ((lower extremit$ or lower limb$) adj5 (ulcer$ or wound$)).ti,ab.
84. or/78-83
85. 77 or 84
86. (or/1-23) and (or/24-71) and 85

This identified 1472 records.

Generic searches

Internet resources and databases Searched: 26 August 2002

Those Internet sites that contained only a few references were simply browsed for relevant papers. Other Internet sites were searched using a search engine/search form. The search interfaces allowed only very simple searching and in most instances a series of keywords were entered and the results scanned for relevant material. Most web interfaces do not offer date restriction and none of the searches were limited by date. There was some duplication between the results and these were removed before all potentially relevant records were entered into an Endnote Library.

Health Evidence Bulletins Wales
no hits
http://www.uwcm.ac.uk/uwcm/1b/pep

Health Services Technology Assessment Text (HSTAT)
no hits
http://text.nlm.nih.gov/

National Coordinating Centre for Health Technology Assessment
1 hit
http://www.hta.nhsweb.nhs.uk

National Guideline Clearinghouse
no hits
http://www.ahcpr.gov/clinic/assess.htm

National Institute for Health and Clinical Excellence (NICE) (published appraisals)
1 hit
http://www.nice.org.uk/nice-web/

Scottish Intercollegiate Guidelines Network (SIGN) Guidelines
1 hit
http://www.sign.ac.uk/

Turning Research Into Practice (TRIP) Index
110 hits
http://www.ceres.uwcm.ac.uk/framset.cfm?section=trip

CD-ROM resources

Health Management Information Consortium (HMIC) Databases; HELMIS 1984–1998/DH-Data & King's Fund Database 1983–2002/King's Fund Database 1979–2002
(searched: 9 November 2002 on ARC SilverPlatter)

1. (neuroisch?emic or isch?emic or diabetic or neuropathic) near3 (foot or feet or ulcer*)
2. (pedal or plantar or foot or feet or heel) near3 (ulcer* or septic or wound*)
3. (foot or feet) near6 diabet*
4. deep foot infection*
5. (crural or leg) near5 ulcer*
6. (venous or stasis or varicos*) near5 (leg or ulcer*)
7. (lower extremit* or lower limb*) near5 (ulcer* or wound*)
8. #1 or #2 or #3 or #4 or #5 or #6 or #7

This identified 189 records.

National Research Register (NRR) (2002, Issue 4) (searched: 12 November 2002)
The National Research Register (NRR) was searched using the CD-ROM interface.

#1 (neuroisch?emic or isch?emic or diabetic or neuropathic) near (foot or feet or ulcer*)
#2 (pedal or plantar or foot or feet or heel) near (ulcer* or septic or wound*)
#3 (foot or feet) near diabet*
#4 deep foot infection*
#5 (crural or leg) near ulcer*
#6 (venous or stasis or varicos*) near (leg or ulcer*)
#7 (lower extremit* or lower limb*) near (ulcer* or wound*)
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

This identified 95 records.

SIGLE (1980–2002 June) (searched: 6 November 2002 on ARC SilverPlatter)

#1 (neuroisch?emic or isch?emic or diabetic or neuropathic) near3 (foot or feet or ulcer*)
#2 (pedal or plantar or foot or feet or heel) near3 (ulcer* or septic or wound*)
#3 (foot or feet) near6 diabet*
#4 deep foot infection*
#5 (crural or leg) near5 ulcer*
#6 (venous or stasis or varicos*) near5 (leg or ulcer*)
#7 (lower extremit* or lower limb*) near5 (ulcer* or wound*)
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7

This identified 43 records.

Results

Number of records retrieved by search type and database

Database	Clinical-effectiveness	Cost-effectiveness	Diagnostic testing
MEDLINE and PREMEDLINE	590	261	1471
EMBASE	449	250	1549
CINAHL	72	85	68
British Nursing Index (BNI)	67	23	54
Allied and Complementary Medicine (AMED)	49	15	44
EconLit	0	3	
HEED	0	77	
NHS EED admin.	0	172	
SIGLE[a]	43		
CDSR	35		
CCTR	176		
DARE admin.	154		
HTA admin.	20		
Controlled Trials	89		
NRR[a]	95		
HELMIS[a]	189		
Total/pre- and post-removal of duplicate citations	2028/1310	886/747	3186/2762

[a] The search strategy covered all three search types: clinical effectiveness, cost-effectiveness and diagnostic testing.

Appendix 2

Expert advisory panel

Members of the expert advisory panel provided feedback on the draft protocol and review.

Dr Jan Apelqvist
Department of Internal Medicine, Lund University Hospital, Sweden

Dr David G. Armstrong
Director of Research and Education, Department of Surgery, Podiatry Section, Southern Arizona Veterans Affairs Medical Center, Tucson, AZ, USA

Professor Andrew Boulton
School of Medicine
University of Manchester
Manchester, UK

Dr Phil Bowler
Wound Care & Prevention Global Development Centre, ConvaTec, Deeside Industrial Park, Flintshire, UK

Dr Gregory Caputo
Center for Locomotion Studies, Pennsylvania State Diabetes Foot Clinics, Pennsylvania State University, University Park
PA, USA

Dr Carol Dealey
Research Fellow, School of Health Sciences, University of Birmingham and University Hospital Birmingham NHS Trust, Research and Development Office, UK.

Ms Jacque Dinnes
Senior Research Fellow, Wessex Institute for Health Research and Development, University of Southampton, UK

Dr Dawn Dowding
Department of Health Sciences/Hull York Medical School, University of York, UK

Ms Madeleine Flanagan
Associate Head of Department, Department of Post-Registration Nursing, University of Hertfordshire, Hatfield, UK

Mr Brian Gilchrist
Head of Pre-registration Education, Florence Nightingale School of Nursing and Midwifery, King's College London, UK

Professor Keith Harding
Department of Rehabilitation Medicine (Wound Healing), University of Wales College of Medicine, Cardiff, UK

Daniel Higman
Consultant Surgeon
Walsgrave Hospital
Coventry, UK

Professor Derek L. Hunt
Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

Ms June Jones
Research Fellow/Clinical Nurse Specialist, Health and Community Care Research Unit (HaCCRU), University of Liverpool, UK

Dr Khalid S. Khan
Education Resource Centre, Birmingham Women's Healthcare NHS Trust, UK

Dr Christopher Lawrence
Newton House, Crick, near Chepstow, UK

Professor DJ Leaper
University Hospital of North Tees, Hardwick, Stockton on Tees, UK

Professor BA Lipsky
Antibiotic Research Clinic, Veterans' Affairs Puget Sound Health Care System and Department of Medicine, University of Washington, Seattle, WA, USA

Dr Astrid K Petrich
Molecular Microbiologist, Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada

Professor Terence J Ryan
Wound Healing Institute, Oxford, UK

Dr Joseph B Selkon
Department of Microbiology, John Radcliffe Hospital, Oxford, UK

Ms Jude Smith
Podiatrist, Department of Podiatry, Selby and York NHS Primary Care Trust, Diabetes Centre, York District Hospital, UK

Dr Steve Thomas
Surgical Materials Testing Laboratory, Princess of Wales Hospital, Bridgend, UK

Dr Carl Thompson
Senior Research Fellow, Department of Health Sciences, University of York, UK

Dr Marie Westwood
Research Fellow, NHS Centre for Reviews and Dissemination, University of York, UK

Mrs Anne Witherow
Altnaglevin Hospital Trust, Londonderry, UK

Mr Peter Jackson (Manchester, UK) and Professor Keith Wilson (York, UK) kindly provided a patient perspective.

Appendix 3

Data extraction forms

Abbreviations used in the following tables are given in the footnote after the final table.

Question 1a: diagnosis of wound infection using clinical examination (diabetic foot ulcer)

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
First author, year, country Study design: case–control, cohort, other? Prospective or retrospective? Method of patient selection (e.g. consecutive, random) Calculation of statistical power Outcomes assessed and methods of data collection used Setting	Eligibility criteria for inclusion in the study Prevalence of disease in the sample Description of study population – spectrum composition	Gender Ethnicity Mean ± SD age Type of diabetes Mean ± SD duration of diabetes Treated with oral anti-diabetic medication/insulin dependent Mean ± SD $HbA1_C$ Body weight/BMI Evidence of neuropathy, and type Evidence of ischaemia, degree and method of assessment (e.g. toe pressure, ABPI, T_CPO_2) or other vascular disease Presence of retinopathy Underlying factors such as nutritional status, immunocompetence, continence, mobility Mean ± SD ulcer area Mean ± SD ulcer depth Mean ± SD ulcer volume Mean ± SD ulcer duration Number of ulcer episodes Grade of ulcer (e.g. Wagner) Previous amputation Presence of necrotic tissue Presence of callus Bacteriology Prior/current use of antimicrobial agents	Index test Provide description of diagnostic index test, i.e. give details of clinical examination methods used. Report number of patients receiving the test Reference test Provide description of reference test used. Report number of patients receiving the reference test and explain how patients were selected if the number is different from those receiving the index test State time lag between the index and reference tests. State who administered the tests	Statistical methods Sensitivity and specificity Likelihood ratios Diagnostic odds ratio Positive and negative predictive values ROC analysis Adverse effects of tests Health-related quality of life Adherence with regimen	Numbers of patients lost to follow-up Reasons for loss to follow-up	Notes about duplicate publication Limitations of the study as noted by authors or reviewer Study sponsorship

Question 1b: diagnosis of wound infection using clinical examination (venous leg ulcer)

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
First author, year, country Study design: case–control, cohort, other? Prospective or retrospective? Method of patient selection (e.g. consecutive, random) Calculation of statistical power Outcomes assessed and methods of data collection used Setting	Eligibility criteria for inclusion in the study Prevalence of disease in the sample Description of study population – spectrum composition	Gender Ethnicity Mean ± SD age Body weight/BMI Presence of co-morbidities, e.g. diabetes Assessment of venous pathology (using reflection rheography, air plethysmography, duplex Doppler ultrasound) Underlying factors such as nutritional status, immunocompetence, continence, mobility Mean ± SD ulcer area Mean ± SD ulcer depth Mean ± SD ulcer volume Mean ± SD ulcer duration Number of ulcer episodes Grade of ulcer Presence of necrotic tissue Bacteriology Prior/current use of antimicrobial agents	Index test Provide description of diagnostic index test, i.e. give details of clinical examination methods used. Report number of patients receiving the test Reference test Provide description of reference test used. Report number of patients receiving the reference test and explain how patients were selected if the number is different from those receiving the index test State time lag between the index and reference tests. State who administered the tests	Statistical methods Sensitivity and specificity Likelihood ratios Diagnostic odds ratio Positive and negative predictive values ROC analysis Adverse effects of tests Health-related quality of life Adherence with regimen	Numbers of patients lost to follow-up Reasons for loss to follow-up	Notes about duplicate publication Limitations of the study as noted by authors or reviewer Study sponsorship

Question 2a: diagnosis – sampling methods (diabetic foot ulcer)

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
First author, year, country Study design: case–control, cohort, other? Prospective or retrospective? Method of patient selection (e.g. consecutive, random) Calculation of statistical power Outcomes assessed and methods of data collection used Setting	Eligibility criteria for inclusion in the study Prevalence of disease in the sample Description of study population – spectrum composition	Gender Ethnicity Mean ± SD age Type of diabetes Mean ± SD duration of diabetes Treated with oral anti-diabetic medication/insulin dependent Mean ± SD $HbA1_C$ Body weight/BMI Evidence of neuropathy, and type Evidence of ischaemia, degree and method of assessment (e.g. toe pressure, ABPI, T_CPO_2) or other vascular disease Presence of retinopathy Underlying factors such as nutritional status, immunocompetence, continence, mobility Mean ± SD ulcer area Mean ± SD ulcer depth Mean ± SD ulcer volume Mean ± SD ulcer duration Number of ulcer episodes Grade of ulcer (e.g. Wagner) Previous amputation Presence of necrotic tissue Presence of callus Bacteriology Prior/current use of antimicrobial agents	Index test Provide description of diagnostic index test, i.e. give details of sampling/specimen collection methods used. Report number of patients receiving the test Reference test Provide description of reference test used. Report number of patients receiving the reference test and explain how patients were selected if the number is different from those receiving the index test State cut-off criterion used. State time lag between the index and reference tests. State who administered the tests Report the following, if data available from the study: type of sample used (tissue, aspirate, fluid, swab) and how it was taken (e.g. swabbing method used); if swab used, state type (e.g. charcoal tipped); wound treatment prior to sampling (e.g. cleansing, debridement); transport medium used; transportation of sample (timing and mode); labelling of sample (clinical detail provided); range of testing used in lab.; whether specific assays or general culture methods used; method of reporting results (quantitative, semi-quantitative, confirmed identification, antibiogram); other interventions performed in conjunction with testing; speed of return of report; speed of antibiotic prescription	Statistical methods Sensitivity and specificity Likelihood ratios Diagnostic odds ratio Positive and negative predictive values ROC analysis Adverse effects of tests Health-related quality of life Adherence with regimen	Numbers of patients lost to follow-up Reasons for loss to follow-up	Notes about duplicate publication Limitations of the study as noted by authors or reviewer Study sponsorship

Question 2b: diagnosis – sampling methods (venous leg ulcer)

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
First author, year, country Study design: case–control, cohort, other? Prospective or retrospective? Method of patient selection (e.g. consecutive, random) Calculation of statistical power Outcomes assessed and methods of data collection used Setting	Eligibility criteria for inclusion in the study Prevalence of disease in the sample Description of study population – spectrum composition	Gender Ethnicity Mean ± SD age Body weight/BMI Presence of co-morbidities, e.g. diabetes Assessment of venous pathology (using reflection rheography, air plethysmography, duplex Doppler ultrasound) Underlying factors such as nutritional status, immunocompetence, continence, mobility Mean ± SD ulcer area Mean ± SD ulcer depth Mean ± SD ulcer volume Mean ± SD ulcer duration Number of ulcer episodes Grade of ulcer Presence of necrotic tissue Bacteriology Prior/current use of antimicrobial agents	Index test Provide description of diagnostic index test, i.e. give details of sampling/specimen collection methods used. Report number of patients receiving the test Reference test Provide description of reference test used. Report number of patients receiving the reference test, and explain how patients were selected if the number is different from those receiving the index test State cut-off criterion used. State time lag between the index and reference tests. State who administered the tests Report the following, if data available from the study: type of sample used (tissue, aspirate, fluid, swab) and how it was taken (e.g. swabbing method used); if swab used, state type (e.g. charcoal tipped); wound treatment prior to sampling (e.g. cleansing, debridement); transport medium used; transportation of sample (timing and mode); labelling of sample (clinical detail provided); range of testing used in lab.; whether specific assays or general culture methods used; method of reporting results (quantitative, semi-quantitative, confirmed identification, antibiogram); other interventions performed in conjunction with testing; speed of return of report; speed of antibiotic prescription	Statistical methods Sensitivity and specificity Likelihood ratios Diagnostic odds ratio Positive and negative predictive values ROC analysis Adverse effects of tests Health-related quality of life Adherence with regimen	Numbers of patients lost to follow-up Reasons for loss to follow-up	Notes about duplicate publication Limitations of the study as noted by authors or reviewer Study sponsorship

Question 3a: diagnosis – laboratory methods (diabetic foot ulcer)

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
First author, year, country Study design: case–control, cohort, other? Prospective or retrospective? Method of patient selection (e.g. consecutive, random) Calculation of statistical power Outcomes assessed and methods of data collection used Setting	Eligibility criteria for inclusion in the study Prevalence of disease in the sample Description of study population – spectrum composition	Gender Ethnicity Mean ± SD age Type of diabetes Mean ± SD duration of diabetes Treated with oral anti-diabetic medication/insulin dependent Mean ± SD $HbA1_C$ Body weight/BMI Evidence of neuropathy, and type Evidence of ischaemia, degree and method of assessment (e.g. toe pressure, ABPI, T_cPO_2), or other vascular disease Presence of retinopathy Underlying factors such as nutritional status, immunocompetence, continence, mobility Mean ± SD ulcer area Mean ± SD ulcer depth Mean ± SD ulcer volume Mean ± SD ulcer duration Number of ulcer episodes Grade of ulcer (e.g. Wagner) Previous amputation Presence of necrotic tissue Presence of callus Bacteriology Prior/current use of antimicrobial agents	Index test Provide description of diagnostic index test, i.e., give details of laboratory techniques used. Report number of samples tested Reference test Provide description of reference test used. Report number of samples tested, and explain how the samples were selected if the number is different from those tested with the index test State cut-off criterion used. State time lag between the index and reference tests. State who administered the tests Report the following, if data available from the study: type of sample used (tissue, aspirate, fluid, swab) and how it was taken (e.g. swabbing method used); if swab used, state type (e.g. charcoal tipped); wound treatment prior to sampling (e.g. cleansing, debridement); transport medium used; transportation of sample (timing and mode); labelling of sample (clinical detail provided); range of testing used in lab.; whether specific assays or general culture methods used; method of reporting results (quantitative, semi-quantitative, confirmed identification, antibiogram); interpretation of molecular tests and appropriateness of controls used; clinician's response to laboratory results; other interventions performed in conjunction with testing; speed of return of report; speed of antibiotic prescription	Statistical methods Sensitivity and specificity Likelihood ratios Diagnostic odds ratio Positive and negative predictive values ROC analysis Adverse effects of tests Health-related quality of life Adherence with regimen	Numbers of patients lost to follow-up Reasons for loss to follow-up	Notes about duplicate publication Limitations of the study as noted by authors or reviewer Study sponsorship

Question 3b: diagnosis – laboratory methods (venous leg ulcer)

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
First author, year, country Study design: case–control, cohort, other? Prospective or retrospective? Method of patient selection (e.g. consecutive, random) Calculation of statistical power Outcomes assessed and methods of data collection used Setting	Eligibility criteria for inclusion in the study Prevalence of disease in the sample Description of study population – spectrum composition	Gender Ethnicity Mean ± SD age Body weight/BMI Presence of co-morbidities, e.g. diabetes Assessment of venous pathology (using reflection rheography, air plethysmography, duplex Doppler ultrasound) Underlying factors such as nutritional status, immunocompetence, continence, mobility Mean ± SD ulcer area Mean ± SD ulcer depth Mean ± SD ulcer volume Mean ± SD ulcer duration Number of ulcer episodes Grade of ulcer Presence of necrotic tissue Bacteriology Prior/current use of antimicrobial agents	Index test Provide description of diagnostic index test, i.e. give details of laboratory techniques used. Report number of samples tested Reference test Provide description of reference test used. Report number of samples tested and explain how the samples were selected if the number is different from those tested with the index test State cut-off criterion used. State time lag between the index and reference tests. State who administered the tests Report the following, if data available from the study: type of sample used (tissue, aspirate, fluid, swab) and how it was taken (e.g. swabbing method used); if swab used, state type (e.g. charcoal tipped); wound treatment prior to sampling (e.g. cleansing, debridement); transport medium used; transportation of sample (timing and mode); labelling of sample (clinical detail provided); range of testing used in lab.; whether specific assays or general culture methods used; method of reporting results (quantitative, semi-quantitative, confirmed identification, antibiogram); interpretation of molecular tests and appropriateness of controls used; clinician's response to laboratory results; other interventions performed in conjunction with testing; speed of return of report; speed of antibiotic prescription	Statistical methods Sensitivity and specificity Likelihood ratios Diagnostic odds ratio Positive and negative predictive values ROC analysis Adverse effects of tests Health-related quality of life Adherence with regimen	Numbers of patients lost to follow-up Reasons for loss to follow-up	Notes about duplicate publication Limitations of the study as noted by authors or reviewer Study sponsorship

Question 4: assessing impact of microbiological analysis on therapy in diabetic foot ulcers

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
First author, year, country Study design: RCT or CCT Method of randomisation (or method of allocation if CCT) Unit of allocation Calculation of statistical power Outcomes assessed and methods of data collection used Setting	Population Inclusion criteria Exclusion criteria	Gender Ethnicity Mean ± SD age Type of diabetes Mean ± SD duration of diabetes Treated with oral anti-diabetic medication/insulin dependent Mean ± SD $HbA1_C$ Body weight/BMI Evidence of neuropathy and type Evidence of ischaemia, degree and method of assessment (e.g. toe pressure, ABPI, T_CPO_2) or other vascular disease Presence of retinopathy Underlying factors such as nutritional status, immunocompetence, continence, mobility Mean ± SD ulcer area Mean ± SD ulcer depth Mean ± SD ulcer volume Mean ± SD ulcer duration Number of ulcer episodes Grade of ulcer (e.g. Wagner) Previous amputation Presence of necrotic tissue Presence of callus Bacteriology Prior/current use of antimicrobial agents	I1: description of strategy 'treat without knowing results of microbiological analysis', giving names of antibiotics or other agents prescribed, with dose, frequency and duration of administration. Also report description of other concomitant interventions used such as topical applications and/or dressings. Report number of patients receiving this strategy I2: description of strategy 'treat after receiving results of microbiological analysis', giving names of antibiotics or other agents prescribed, with dose, frequency and duration of administration. Also report description of other concomitant interventions used such as topical applications and/or dressings. Report number of patients receiving this strategy State speed of return of report and speed of antibiotic prescription	Statistical methods Mortality (all) Mortality (related to amputation) Amputation (incidence and type, e.g. major/minor) Incidence of osteomyelitis Number/duration of hospital admissions for DFU problems Proportion of patients achieving complete healing Time to complete healing Change in ulcer area (absolute or percentage values) Remaining wound area Healing rate (absolute or relative) Change in ulcer depth (absolute or relative) Change in ulcer volume (absolute or relative) Recurrence of ulcer Pain (in patients without neuropathy) Bacterial profile Acquisition of resistant organisms Relationship between ulcer healing and bacteriology Change in mobility Change in level of dependence Adverse events Quality of life Adherence with treatment regimen	Numbers of withdrawals per treatment group Reasons for withdrawal	Notes about duplicate publication Limitations of the study as noted by authors or reviewer Study sponsorship

Question 5a: assessing clinical effectiveness of therapy in diabetic foot ulcers

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
First author, year, country Study design: RCT or CCT Method of randomisation (or method of allocation if CCT) Unit of allocation Calculation of statistical power Outcomes assessed and methods of data collection used Setting	Population Inclusion criteria Exclusion criteria	Gender Ethnicity Mean ± SD age Type of diabetes Mean ± SD duration of diabetes Treated with oral anti-diabetic medication/insulin dependent Mean ± SD $HbA1_C$ Body weight/BMI Evidence of neuropathy and type Evidence of ischaemia, degree and method of assessment (e.g. toe pressure, ABPI, T_CPO_2) or other vascular disease Presence of retinopathy Underlying factors such as nutritional status, immunocompetence, continence, mobility Mean ± SD ulcer area Mean ± SD ulcer depth Mean ± SD ulcer volume Mean ± SD ulcer duration Number of ulcer episodes Grade of ulcer (e.g. Wagner) Previous amputation Presence of necrotic tissue Presence of callus Bacteriology Prior/current use of antimicrobial agents	I1: description of antimicrobial agent used, giving names of antibiotics or other agents prescribed, with dose, frequency and duration of administration. Also report description of other concomitant interventions used such as topical applications and/or dressings. Report numbers of patients receiving this regimen I2: description of alternative antimicrobial agent used, as above. Report numbers of patients receiving this regimen C: description of control regimen, e.g. standard care, giving details of any agents prescribed, with dose, frequency and duration of administration. Also report description of other concomitant interventions used such as topical applications and/or dressings. Report numbers of patients receiving this regimen	Statistical methods Mortality (all) Mortality (related to amputation) Amputation (incidence and type, e.g. major/minor) Incidence of osteomyelitis Number/duration of hospital admissions for DFU problems Proportion of patients achieving complete healing Time to complete healing Change in ulcer area (absolute or percentage values) Remaining wound area Healing rate (absolute or relative) Change in ulcer depth (absolute or relative) Change in ulcer volume (absolute or relative) Recurrence of ulcer Pain (in patients without neuropathy) Bacterial profile Acquisition of resistant organisms Relationship between ulcer healing and bacteriology Change in mobility Change in level of dependence Adverse events Quality of life Adherence with treatment regimen	Numbers of withdrawals per treatment group Reasons for withdrawal	Rationale for defining the study agent as an antimicrobial agent, if necessary Notes about duplicate publication Limitations of the study as noted by authors or reviewer Study sponsorship

Question 5b: assessing the cost-effectiveness of treatment in diabetic foot ulcers

Study identifier and objective	Key elements of the study	Clinical effectiveness data	Economic analysis	Results	Comments
First author, year, country Objective(s) of the study	Type of economic evaluation, e.g. CEA, CUA, CBA Perspective, e.g. NHS, patient, insurance company, society Settings of clinical effectiveness study and economic evaluation Specify dates to which data relate for clinical effectiveness data, resource use and prices used	State sources, e.g. single study, synthesis of studies, expert opinion/authors' assumptions, combination of above. Specify study design, e.g. RCT, systematic review and methods of data analysis used (e.g. intention-to-treat) Participants – describe characteristics Interventions – provide details of interventions/regimens used Clinical outcomes assessed, including adverse effects Brief description of results If single study used, describe link between clinical effectiveness and cost data	Measure of health benefits used Description of costs (separate descriptions for direct and indirect costs), including specific costs taken into account, source of cost data/methods of estimation, discounting (if applicable) Currency Methods used for statistical analysis of quantities and costs Method used for sensitivity analyses (e.g. one-way or multi-way analysis); describe relevant variables and any assumptions used Describe models (if any) used for estimation of benefits and/or costs	Report estimated health benefits Report estimated costs Report results of synthesis of costs and benefits, e.g. incremental cost–utility of treatment Report results of sensitivity analyses, and describe the range of values derived	Notes about duplicate publication Limitations of the study – comment on the following: choice of comparator; validity of estimates of effectiveness, health benefits and costs; external validity of findings; authors' own notes about limitations of the study. State whether the authors' conclusions were justified given the limitations of the study Study sponsorship

ABPI, ankle brachial pressure index; BMI, body mass index; C, control group; CBA, cost–benefit analysis; CCT, controlled clinical trial; CEA, cost–effectiveness analysis; CUA, cost-utility analysis; DFU, diabetic foot ulcer; $HbA1_C$, glycosylated haemoglobin concentration; I1, first intervention group; I2, second intervention group; RCT, randomised controlled trial; ROC, receiver operating characteristic; SD, standard deviation; T_CPO_2, transcutaneous pressure of oxygen.

Appendix 4

Data extraction tables

Diagnosis data extraction

Study and design	Participants	Baseline characteristics	Test details	Results	Withdrawals	Comments
Gardner (2001),[90,95,145] USA Study design: Cross-sectional Method of patient selection: Not stated Outcome assessment: A dry gauze dressing was applied to the wound and left in place for 1 hour in order to standardise conditions for assessing wound exudate. After 1 hour, the dressing was removed and the wound and dressing were assessed using the CSSC. This step was repeated independently by a second nurse rater Setting – 4 centres. Site A – acute care veterans' facility outpatients clinics;	Inclusion criteria: Sites A–C: $n = 26$ (A 20, B 4, C 2): Age at least 18 years; presence of full-thickness, non-arterial chronic wound; white blood cell count >1500 cells/mm^3 or total lymphocyte count >800 cells/mm^3; platelet count >125,000/mm; no coagulopathies, not on anticoagulation therapy Site D: $n = 10$ Age at least 18 years; presence of non-arterial chronic wound; wound biopsy performed within 8 hours of data collection Non-arterial chronic wounds were defined as wounds associated with venous insufficiency,	36 participants recruited Gender: M 31 (86%), F 5 (14%) Ethnicity: Caucasian: 35 (97%) Number of wounds per participant: One chronic wound: 23 (63%) Two chronic wounds: 6 (17%) Three chronic wounds: 6 (17%) Four chronic wounds: 1 (3%) For participants with more than one wound, a single wound was selected randomly for study. Verified infection status: 11 patients had positive wound biopsy 25 patients had negative wound biopsy Characteristics for total sample; infected and non-infected groups: Mean ± SD age: Total 65.1 ± 13.2; Inf. 64.5 ± 16.9; Non- Inf. 65.4 ± 11.5 Setting: Site A 20 (56%); 1 (9%); 19 (76%) Site B 4 (11%); 0 (0%); 4 (16%) Site C 2 (5%); 0 (0%); 2 (8%) Site D 10 (28%); 10 (91%); 0 (0%) Diabetes: None 20 (56%); 6 (55%); 14 (56%) Type 1 2 (5%); 1 (9%); 1 (4%) Type 2 14 (39%); 4 (36%); 10 (40%) Nutritional parameters (mean ± SD): Red blood cells 3.89 ±0.66; 4.06 ± 0.78; 3.83 ± 0.63 White blood cells 9.1 ± 5.3 ($n = 33$); 9.2 ± 5.0 ($n = 8$); 9.1 ± 5.5 ($n = 25$) Albumin 3.4 ± 0.7 ($n = 32$); 3.5 ±0.8 ($n = 7$); 3.4 ±0.7 ($n = 25$) Total protein 6.9 ± 0.9 ($n = 30$); 7.6 ± 0.5 ($n = 5$); 6.8 ± 0.9 ($n = 25$)	Index test: Using a CSSC, 5 individual classic signs and symptoms of acute infection in chronic wounds were evaluated (pain, erythema, oedema, heat and purulent exudate), plus 6 individual signs and symptoms specific to infection in secondary wounds (serous exudate plus concurrent inflammation, delayed healing, discoloration of granulation tissue, friable granulation tissue, foul odour, and wound breakdown). 36 patients received the test Reference test: Quantitative culture of viable wound tissue according to procedures outlined by Stotts.[175] Wound cleansed with normal saline using sterile technique. Approx.1 g of non-necrotic, viable wound tissue obtained from the centre of the ulcer using 3 or 4 mm dermal punch under sterile conditions. Tissue transported immediately to microbiology laboratory. Methods of	The study authors reported 2 × 2 diagnostic data for each of 11 clinical signs and symptoms of chronic wound infection, as follows: Increasing pain Biopsy + – Total CSSC + 4 0 4 – 7 25 32 Total 11 25 36 Erythema Biopsy + – Total CSSC + 6 8 14 – 5 17 22 Total 11 25 36 Oedema Biopsy + – Total CSSC + 7 7 14 – 4 18 22 Total 11 25 36 Heat Biopsy + – Total CSSC + 2 4 6 – 9 21 30 Total 11 25 36	No withdrawals were reported	Limitations of the study as noted by authors: Cross-sectional study design precludes cause and effect relationship analysis. Reliability of the CSSC needs further exploration with a larger, more representative sample of clinicians. Generalisability of findings limited owing to non-probability sampling used. The enrolled participants might not be representative of all chronic wound patients, and only 70% of eligible patients took part in the study. Agreement between clinicians not accounted for in estimates of validity (estimates based on assessment of only one observation).

continued

Study and design	Participants	Baseline characteristics	Test details	Results	Withdrawals	Comments
Site B – veterans' long-term care facility; Site C – veterans' inpatient facility with nursing home beds, rehabilitation beds and intermediate psychiatry beds; Site D – university-based medical centre chronic wound clinic serving inpatients and outpatients	peripheral neuropathy, surgical incision, or trauma, with adequate arterial perfusion as determined by palpable local pulses or ankle-brachial index >0.5)	Receiving systemic antibiotics at time of recruitment: No 24 (67%) 10 (91%) 14 (56%) Yes 12 (33%) 1 (9%) 11 (44%) Receiving anti-inflammatory medication at time of recruitment: No 20 (56%) 9 (82%) 11 (44%) Yes 16 (44%) 2 (18%) 14 (56%) Receiving steroid medication at time of recruitment: No 33 (92%) 10 (91%) 23 (92%) Yes 3 (8%) 1 (9%) 2 (8%) Wound type: Pressure ulcer 19 (53%) 3 (27%) 16 (64%) Venous ulcer 7 (19%) 4 (37%) 3 (12%) Secondary incision 6 (17%) 2 (18%) 4 (16%) Chronic traumatic 2 (5.5%) 1 (9%) 1 (4%) Diabetic ulcer 2 (5.5%) 1 (9%) 1 (4%) Wound size: Mean ± SD area (cm^2) 4.5 ± 6.9 5.5 ± 6.1 4.1 ± 7.3 Mean ± SD depth (cm) 1.3 ± 1.6 0.8 ± 0.9 1.4 ± 1.8 Mean ± SD wound duration (days): 616.6 ±1742.8 1002 ±2673.3 447.1 ±1163.6 Number (%) of patients with necrotic tissue: None 15 (42%) 1 (9%) 14 (56%) <25% 9 (25%) 5 (45%) 4 (16%) 25–50% 8 (22%) 4 (36%) 4 (16%) >50 and <75% 3 (8%) 1 (9%) 2 (8%) 75–100% 1 (3%) 0 (0%) 1 (4%) Type of topical agents in use: None 24 (67%) 7 (64%) 17 (68%) Growth factor 4 (11%) 1 (9%) 3 (12%) Silver sulfadiazine 4 (11%) 1 (9%) 3 (12%) Antibiotic 3 (8%) 2 (18%) 1 (4%) Wound gel 1 (3%) 0 (0%) 1 (4%)	laboratory culturing followed those of Krizek and Robson [176] Tissue was weighed, homogenised and serially diluted and plated. Each series of dilutions was plated under aerobic and anaerobic conditions. Organisms were identified using standard microbiological procedures. 36 patients received the test Infected ulcers were defined as those having at least 10^5 organisms per gram of viable tissue or wounds containing haemolytic *Streptococcus* at any level. Non-infected ulcers were defined as those with specimens containing less than 10^5 organisms per gram of tissue Timing: At sites A, B and C, tissue biopsy was obtained less than 1 hour after assessment with the CSSC. At site D, the wound biopsy was performed within 8 hours of assessment with CSSC Assessment of inter-rater reliability: The inter-rater reliability	Purulent exudate Biopsy + – Total CSSC + 2 9 11 – 9 16 25 Total 11 25 36 Serous exudate plus concurrent inflammation Biopsy + – Total CSSC + 6 7 13 – 5 18 23 Total 11 25 36 Delayed healing Biopsy + – Total CSSC + 9 9 18 – 2 16 18 Total 11 25 36 Discolouration Biopsy + – Total CSSC + 7 11 18 – 4 14 18 Total 11 25 36 Friable granulation Biopsy + – Total CSSC + 9 6 15 – 2 19 21 Total 11 25 36		Mixture of wounds/small sample precluded analysis by type of wound Study sponsorship: part funding by National Pressure Ulcer Advisory Panel, Knoll Pharmaceutical, The Gerontological Nursing Intervention Center, the VA Predoctoral Nurse Fellowship Program, Office of Academic Affiliations, Department of Veterans Affairs, an Institutional NRSA fellowship (Research Training in Gerontological Nursing) from the National Institute of Nursing Research, National Institutes of Health, an Institutional NRSA fellowship (Interdisciplinary Research Training Program on Aging) from the National

continued

Study and design	Participants	Baseline characteristics	Test details	Results	Withdrawals	Comments
			of the items on the checklist was assessed using wound observations made independently by the principal investigator and one of five specifically trained nurses representing each study site. The κ range was 0.53–1.00. No agreement was found for one clinical sign (pocketing of the wound base) due to non-occurrence of the sign in the study sample. Therefore, the diagnostic performance of this sign was not evaluated	Foul odour Biopsy + – Total CSSC + 4 3 7 – 7 22 29 Total 11 25 36 Wound breakdown Biopsy + – Total CSSC + 5 0 5 – 6 25 31 Total 11 25 36 Results for total sample (n = 36) Sensitivity and specificity of each sign or symptom (calculated by study authors and checked by reviewer): Se Sp Increasing pain 36% 100% Erythema 55% 68% Oedema 64% 72% Heat 18% 84% Purulent exudate 18% 64% Serous + inflammation 55% 72% Delayed healing 81% 64% Discoloration 64% 56% Friable granulation 82% 76% Foul odour 36% 88% Wound breakdown 46% 100% Predictive values (PPV calculated by study authors and checked by reviewer; NPV calculated by reviewer):		Institute on Aging, National Institutes of Health

continued

Study and design	Participants	Baseline characteristics	Test details	Results	Withdrawals	Comments
				PPV NPV Increasing pain 100% 78% Erythema 43% 77% Oedema 50% 82% Heat 33% 70% Purulent exudate 18% 64% Serous + inflammation 46% 78% Delayed healing 50% 89% Discoloration 39% 78% Friable granulation 60% 90% Foul odour 57% 76% Wound breakdown 100% 81% Likelihood ratios (+LR calculated by study authors and checked by reviewer/–LR calculated by reviewer): +LR –LR Increasing pain 18.18 0.64 Erythema 1.71 0.67 Oedema 2.27 0.5 Heat 1.14 0.97 Purulent exudate 0.51[a] 1.28[a] Serous + inflammation 1.95 0.63 Delayed healing 2.27 0.28 Discoloration 1.45 0.65 Friable granulation 3.41 0.24 Foul odour 3.03 0.72 Wound breakdown 22.73 0.55		

continued

Study and design	Participants	Baseline characteristics	Test details	Results	Withdrawals	Comments
				Results for patients with venous leg ulcers (n = 7) Sensitivity (calculated by study authors, reviewer unable to check as 2 × 2 data not provided): Increasing pain 5% Erythema 50% Oedema 100% Heat 25% Purulent exudate 67% Serous + inflammation 25% Delayed healing 100% Discoloration 25% Friable granulation 75% Foul odour 25% Wound breakdown 75%		

CSSC, clinical signs and symptoms checklist; F, female; Inf, infected; LR, likelihood ratio; M, male; Non-inf, non-infected; NPV, negative predictive value; PPV, positive predictive value; SD, standard deviation; Se, sensitivity; Serous + inflammation, serous exudate plus concurrent inflammation; Sp, specificity; Tot, total.

[a] For purulent exudate, the values for LRs are the opposite to what would normally be expected, that is, the +LR in this case is less than 1 and the –LR is greater than 1. This may be explained as follows. For the +LR, the ratio is derived from the very low sensitivity for this clinical sign (18%) and the relatively high number of false positives expressed as a proportion of the total without disease as verified by the reference standard. For the –LR the ratio is derived from the large proportion of false negatives relative to the total with disease and the specificity of 64%. These findings are as would be expected for a test that excludes disease as opposed to identifying it. The conclusion from these data is that purulent exudate is a very poor test of the presence of infection and that absence of this clinical sign is more likely to indicate infection than its presence.

Study and design	Participants	Baseline characteristics	Test details	Results	Withdrawals	Comments
Ratliff (2002),[92] USA Study design: Prospective cohort Method of patient selection: Patients were recruited who attended the clinic from November 2001 to April 2002 Outcome assessment: 2 × 2 diagnostic data were reported for different criteria to define infection using semi-quantitative analysis techniques Setting: University-based wound care clinic	Eligibility criteria for inclusion in the study: Patients with wounds present for more than 6 months (could include any type of cutaneous wound at any body site) Exclusion criteria: Wounds with gross surface contamination, necrotic tissue, purulent drainage or eschar	*n* = 124 wounds on 124 patients Gender: male 74, female 50 Mean age: Not reported Type of diabetes: Not reported Wound type: Pressure ulcers 44 Venous ulcers 27 Neuropathic or diabetic ulcers 29 Lower extremity arterial ulcers 8 Other aetiologies 16	Wound treatment prior to sampling: The wound was cleaned to remove surface contamination using a sterile 4 × 4 cm gauze moistened with sterile saline Index test: semi-quantitative analysis (124 patients): Using sterile technique, an alginate-tipped applicator was rotated over a 1 cm^2 area for 5 seconds with sufficient pressure to cause tissue fluid to be expressed. The tip of the swab was broken off into a sterile transport tube. The sample was transported immediately to the laboratory for processing. The swab was processed using a semi-quantitative technique. A blood agar plate was streaked three times on one quadrant and then three times on each remaining quadrant in sequence (I, II, III, IV) using a sterile loop for each quadrant, in order to create dilutions of the original swab in each quadrant. The more bacteria on the original swab, the more quadrants showing bacterial growth. All plated specimens were incubated under aerobic conditions at 37°C. After 24 hours, the plates were visually inspected and colonies of bacteria counted in the four quadrants	2 × 2 table for semi-quantitative definition of infection as growth in quadrant III or quadrants III and IV: Quantitative: + / – / Total Semi-quant. +: 42 / 7 / 49 Semi-quant. –: 11 / 64 / 75 Total: 53 / 71 / 124 Sensitivity 79% Specificity 90% Other measures (calculated by reviewer): PPV 86% NPV 85% +LR 8.04 –LR 0.23 2 × 2 table for semi-quantitative definition of infection as growth in quadrant II, quadrants II and III or quadrants II, III and IV: Quantitativ: + / – / Total Semi-quant. +: 53 / 26 / 79 Semi-quant. –: 0 / 45 / 45 Total: 53 / 71 / 124 Derived measures (calculated by reviewer): Sensitivity 100% Specificity 63% PPV 67% NPV 100% +LR 2.73 –LR 0.015	There were no withdrawals	Suggestions for future research, as suggested by the authors: Comparison of cotton-tipped swabs and calcium alginate-tipped swabs should be performed (alginate swabs were used in this study because cotton-tipped swabs may be bacteriostatic secondary to the oxidative sterilisation procedure; alginate swab is more expensive than cotton swab) Limitations of the study as noted by reviewer: Mixed population in terms of wound aetiology Study sponsorship: Not stated

continued

Study and design	Participants	Baseline characteristics	Test details	Results	Withdrawals	Comments
			Reference test: quantitative analysis (124 patients): Following the acquisition of the swab sample for semi-quantitative analysis, another swab was obtained from the same site using the same technique. The tip of the swab was broken off and placed into a sterile transport tube containing 5 ml of normal saline. The sample was transported immediately to the laboratory for processing. The swab was processed using a quantitative technique. Serial dilutions of the swabs were performed and plated on sterile agar medium. All plated specimens were incubated under aerobic conditions at 37°C. After 24 hours, the plates were visually inspected and colonies of bacteria counted. CFUs were utilised to determine the total bacterial count on each plate Soft tissue infection was defined as the presence of $>10^5$ CFU cm^2 Timing: The swab for quantitative analysis was obtained after the swab for semi-quantitative analysis. The time interval between the acquisition of the two specimens was not stated	2 × 2 table for semi-quantitative definition of infection as growth in quadrant I, quadrants I and II, quadrants I, II and III or quadrants I, II, III and IV: Quantitative: + / – / Total Semi-quant +: 53 / 45 / 98 Semi-quant –: 0 / 26 / 26 Total: 53 / 71 / 124 Derived measures (calculated by reviewer): Sensitivity 100% Specificity 37% PPV 54% NPV 100% +LR 1.58 –LR 0.026 2 × 2 table for semi-quantitative definition of infection as growth in quadrants I, II, III and IV: Quantitative: + / – / Total Semi-quant. +: 14 / 1 / 15 Semi-quant. –: 39 / 70 / 109 Total: 53 / 71 / 124 Derived measures (calculated by reviewer): Sensitivity 26% Specificity 99% PPV 93% NPV 64% +LR 18.75 –LR 0.75		

Study and design	Participants	Baseline characteristics	Test details	Results	Withdrawals	Comments
Bill (2001),[91] USA Study design: Cross-sectional Method of patient selection: Consecutive Outcome assessment: Correlation between results of quantitative wound biopsy and swab culture Setting: University-based, multidisciplinary chronic wound centre	Eligibility criteria for inclusion in the study: Willing participants with informed consent. Any cutaneous wound, at any body site, present for more than 6 months. (Patients with gross surface contamination of the wound, necrotic tissue, purulent drainage or eschar were not cultured)	$n = 38$ Gender: M 25, F 13 Ethnicity: African–American: 12 Caucasian: 26 Mean age: 59 years Type of diabetes: Not stated Wound type: Pressure ulcers 18 Lower extremity diabetic wounds 10 Wounds secondary to venous stasis disease 5 Arterial ulcers 5	Wound treatment prior to sampling: A sterile 4 ×4 cm gauze was moistened with sterile saline and the wound surface wiped vigorously to remove surface contamination. If >1 wound was present per patient, the largest was selected for study Index test: Swab culture (38 patients): using a sterile technique, an alginate-tipped applicator rotated over a 1 ×1 cm area for 5 seconds with sufficient pressure to express tissue fluid. Sample taken from the centre of the wound. Tip of the swab broken off into a sterile transport tube containing 5 ml of saline. Serial dilutions of swab sample performed and plated on sterile agar medium Reference test: wound biopsy (38 patients): 5 mm punch biopsy was taken from the centre of the swab site. Sterile forceps used to transfer the sample to the transport vial before immediate transfer to the laboratory. Tissue biopsy samples weighed and homogenised with a sterile tissue grinder before being plated on a sterile agar medium All plated specimens incubated under aerobic conditions (37°C). After 24 hours, plates visually inspected and bacteria colonies counted. CFUs used to determine total bacterial count of each plate Authors defined soft tissue infection $>10^5$ CFUs g of tissue for quantitative wound biopsy and $>10^5$ CFUs cm^2 for swab culture. Timing: biopsy followed immediately after swab culture obtained	2 × 2 table: Biopsy + – Total Swab + 22 4 26 – 6 6 12 Total 28 10 38 Derived measures (calculated by reviewer): Sensitivity 79% Specificity 60% PPV 85% NPV 50% +LR 1.96 –LR 0.36	Number of patients lost to follow-up: none	Limitations of the study as noted by authors: further research should include more patients with larger number of wound aetiologies Limitations of the study as noted by reviewer: the small number of patients recruited overall and the heterogeneous nature of the group with regard to wound type mean that the derived diagnostic measures should be interpreted with great caution The study authors were contacted and requested to provide 2 × 2 diagnostic data on the patients with DFUs, but data were unavailable

Effectiveness data extraction tables

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Apelqvist (1996),[122,126] Sweden Study design: RCT, open design Method of randomisation: Computer-generated list. Patients were stratified according to size and type of the ulcer (Wagner grade 1 or 2) Unit of allocation: Patient Calculation of statistical power: Not described Outcome assessment: Patients were examined at the end of weeks 1, 4, 8 and 12. Colour photographs with scales were taken at the visits to the foot care team. Photographs were evaluated blind at the end of the study by two independent physicians. In the event of disagreement in the evaluation of photographs, the assessment by the foot care team was decisive. The outcome was classified as successful if the initial ulcer area was reduced by >50% or an	Inclusion criteria: Caucasian, >40 years old, with a history of diabetes mellitus and an exuding cavity ulcer below the ankle (Wagner grade 1 or 2) with ulcer area >1 cm^2 and systolic toe pressure >30 mmHg or systolic ankle pressure >80 mmHg Wagner grade 1 was classified as a superficial ulcer breaking through subcutaneous tissue and grade 2 as a deep ulcer Only one ulcer was studied in each patient. If there were several ulcers, the largest fulfilling the inclusion criteria was chosen Exclusion criteria: Patients with ulcer area >25 cm^2, presence of deep abscess, osteomyelitis, or gangrene (Wagner grade 3 or 4),	Baseline characteristics were not reported in detail; however, the authors stated that there were no major differences between the two treatment groups in clinical characteristics All patients had signs of severe sensory neuropathy, and in all except two cases, a precipitating cause of the ulcer was seen, of which mechanical stress was the most common (n = 27) Approximately 50% of patients had previous amputations, mostly due to deep infection prior to inclusion	I: Topical treatment with cadexomer iodine ointment (Iodosorb®). Dressings were changed once daily during the first week and daily or every second or third day during the following weeks depending on the degree of exudation (n = 22) C: Standard topical treatment consisting of: gentamicin solution 80 mg/ml (Garamycin®, Schering-Plough), prescribed twice daily if an ulcer was infected (i.e. cellulitis present); streptodornase/streptokinase (Varidase®, Lederle), used for moist, necrotic lesions, changed twice daily; or dry saline gauze (Mesalt®), used as an absorptive dressing and changed once or twice daily according to the degree of exudation (n = 19) All patients: Oral antibiotics (ciprofloxacin, cephalosporins, metronidazole, clindamycin) were used if signs of infection (i.e. cellulitis) were present. The ulcers were cleaned with sterile saline and dressed according to the manufacturers' recommendations by the usual nursing staff. When ulcers were no longer producing exudate, vaseline gauze (Jelonet®, Smith	Statistical methods: Differences between or within groups were tested using the Mann–Whitney U–test (two-tailed). The analysis was based on treatment completers only (18 in C and 17 in I). The authors reported no major differences between the two groups in outcomes at 12 weeks. p-Values of the differences were not reported Surgical revision performed: I: 3/17 (18%) C: 5/18 (28%) Complete healing: I: 5/17 (29%) C: 2/18 (11%) Wound area reduction of >50% or improvement in Wagner grade: I: 12/17 (71%) C: 13/18 (72%) Adverse effects: The authors reported that none were documented	Withdrawals: C: 4/22 (18%) I: 2/19 (11%) Reasons for withdrawal (not reported per group): Violation of inclusion criteria n = 2 Hospitalisation n = 2 Non-adherence n = 1 Insufficient data on resource use n = 1	Note: the data shown here are taken from two papers [122,126] Eligibility of the intervention for this review: The authors describe cadexomer iodine ointment as being "highly fluid-absorbing, *antibacterial* and able to dissolve debris and necrotic tissue", and provide supporting references Study sponsorship: Perstorp Pharma, Lund, Sweden, and the Swedish Diabetes Association

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
improvement in Wagner grade was seen. Healing was defined as intact skin. Ulcer area was measured by multiplying maximum length by maximum width Setting and length of treatment: Single-centre study. Outpatients department, involving a multidisciplinary foot care team (diabetologist, orthopaedic surgeon, orthotist, podiatrist, diabetes nurse). Trial duration 12 weeks	undergoing thyroid gland investigations, unlikely to adhere with study protocol were excluded Patients were withdrawn from the study in the case of hospitalisation, lack of adherence, ulcer deterioration (Wagner grade 3 or 4), >100% increase in ulcer area or adverse reactions to the topical treatment		& Nephew Medical) was applied Prior to inclusion, footwear was corrected or special footwear provided if local pressure relief was required			

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Bouter (1996),[106] The Netherlands Study design: RCT, open Method of randomisation: Computer-generated random numbers table Unit of allocation: Patient Calculation of statistical power: Not reported Outcome assessment: Patients were examined at baseline, completion of antibiotic treatment, and every 3 days during therapy. X-ray of the affected limb was done at study entry and during study period if indicated. Clinical response to treatment was assessed after completion of antibiotic therapy and was classified as cured (disappearance of the initial infection), improved (initial infection under control), failure (persistence or aggravation of initial infection, requiring change of therapy), or death. Blood cultures and wound cultures (using purulent	Population: Patients hospitalised for diabetic foot lesions with Wagner classifications of 2, 3 and 4 in the Bosch MediCentre, Den Bosch and the Eemland Hospital, Amersfoort, The Netherlands Inclusion criteria: Ankle/brachial index of at least 0.45 (derived by dividing the ankle systolic pressure by the brachial artery systolic pressure); normal renal and liver function Exclusion criteria: Hypersensitivity to any of the study drugs; received antimicrobial therapy effective against the infecting pathogens within 48 hours prior to study treatment; high probability of death within 48 hours; infection with microorganisms resistant to the study drugs	Numbers male/female: I1: 8/14 I2: 12/12 Mean ± SD age (years): I1: 71.9 ± 8.2 I2: 70.9 ± 11.3 Numbers with Type 1/Type 2 diabetes: I1: 2/20 I2: 3/21 Mean ± SD duration of diabetes (years): I1: 9.9 ± 8.6 I2: 11.3 ± 6.4 Numbers classified as Wagner 2/3/4: I1: 9/9/4 I2: 9/9/6 Mean ± SD ankle brachial index: I1: 0.70 ± 0.23 I2: 0.71 ± 0.22 Background heart disease (%): I1: 33.3 I2: 54.2 Retinopathy (%): I1: 59.1 I2: 33.3 Nephropathy (%): I1: 54.5 I2: 54.2 Neuropathy (%): I1: 45.5 I2: 54.2	I1: I/C 500 mg q.d.s i.v. Minimum duration of treatment was 10 days (n = 22) The dose of imipenem was reduced in cases of renal dysfunction (500 or 250 mg b.d.) I2: Piperacillin 3000 mg q.d.s. i.v. in combination with clindamycin 600 mg t.d.s. i.v. Minimum duration of treatment was 10 days (n = 24) The dose of piperacillin was reduced in cases of renal dysfunction (2000 or 1000 mg q.d.s.). The dose of clindamycin was reduced in cases of liver dysfunction. (Reviewer's note: it is presumed that, since participants had to have normal renal function to be included in the trial, the reduced doses were administered if renal dysfunction was detected during the study period) All patients: Antibiotic therapy was discontinued if the patient's clinical condition worsened after 72 hours. Patients were restricted to bed rest during therapy and thrombolytic treatment was prescribed. Topical application of antibiotics was not permitted. In cases of	Statistical methods: χ^2 test with Yate's correction or Fisher's exact test (both two-tailed) No patients received concomitant systemic or topical antibiotics Mean ± SD duration of therapy (days): I1: 23.6 ± 11.5 I2: 24.3 ± 20.6 The foot infections were polymicrobial in 55% of cases. *Staphylococcus aureus* was cultured in 16 patients, haemolytic streptococci in 8 patients and enterococci in 10 patients. Enterobacteriaceae were isolated from 17 and anaerobes from 4 patients. *Pseudomonas* species were not cultured at the time of admission in any patient although *Xanthomonas maltophilia* was cultured in one patient with a superinfection Numbers (%) with clinical response to treatment I1/I2: Cured: 4 (19.0)/6 (25.0) Improved: 16 (76.2)/12 (62.2) Failed: 0/2 (8.3) Died: 1 (4.8)/4 (16.7) The authors reported that none of the differences in clinical outcomes of the two study groups were statistically significant. However, p-values were not reported	One patient in I1 was inadvertently included twice and was therefore not evaluable For analysis of bacteriological response to treatment: One patient in each group was not evaluable owing to a negative baseline culture	Study sponsorship: Not stated It is not clear whether all patients received antibiotic therapy for the stipulated minimum treatment period of 10 days

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
discharge, infected tissue or superficial swabs if former materials not available) were obtained prior to enrolment. Gram stains were performed routinely on specimens from all sites with known or presumed infection. Bacteriological response of baseline pathogens was recorded 3–5 days after starting therapy and 1–3 days after completion of treatment. Response was classified as eradication, partial eradication, failure, superinfection, relapse (after completion of therapy) or non-evaluable owing to negative baseline culture. All observed and monitored adverse effects were recorded and classified as mild, moderate or severe. Haematology and biochemistry were performed at 2–3 days after enrolment and 3–days after completion of therapy Setting and length of treatment: Hospital. Minimum treatment duration 10 days			chronic osteomyelitis, antibiotic therapy was continued with ciprofloxacin 500 mg b.d. orally or ofloxacin 400 mg b.d. orally and/or clindamycin 600 mg t.d.s. depending on culture results	Mortality: I1: One patient died of background heart disease while his diabetic foot was considered to be clinically improved I2: Four patients died overall. In two patients, diabetic foot infection was considered to be the cause of death. One patient died of background cardiovascular disease while the condition of his diabetic foot was considered to be improved. One other patient died of background cardiovascular disease before amelioration of the diabetic foot could be reported Numbers (%) with bacteriological response to treatment I1/I2: Eradication: 9 (45.0)/16 (70.0) Partial eradication: 3 (15.0)/1 (4.3) Failure: 1 (5.0)/3 (13.0) Superinfection: 4 (20.0)/3 (13.0) Relapse: 3 (15.0)/0 The authors reported that differences in between groups were not statistically significant Numbers (%) experiencing adverse events probably related to study drugs: I1: 3 (19.0) I2: 12 (50.0) $p < 0.05$ Classifications of severity of adverse events (mild/moderate/severe) was not reported as described in the methods		

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
				Diarrhoea was the single most reported adverse effect ($n = 4$); *Clostridium difficile* toxin was detected in one of these patients. In I2 one patient developed vasculitis that was ascribed to the use of clindamycin. Increased liver enzymes were observed in another patient. In I1 one patient experienced *Candida* stomatitis and 2 patients complained of nausea. *Candida* stomatitis was also observed in one patient in I2. NB: it was not clear from the text which adverse events occurred in which group		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Bradsher (1984),[43] USA Study design: RCT Method of randomisation: Random number code Unit of allocation: Patient Calculation of statistical power: Not reported Outcome assessment: Culture and sensitivity of material from infection sites were performed before initiation of therapy and every 2–3 days during therapy until culture negative or conclusion of therapy (anaerobic cultures not routinely taken). Results of bacteriological assessment were classified as elimination (no further isolation of pathogen), reduction (decreased number of same organism on subsequent cultures), persistent (same or greater numbers of the original organism), relapse (return of the original organism after completion of therapy), reinfection (isolation of a separate pathogenic organism with clinical	Population: Adults with suspected serious bacterial skin and soft tissue infections, hospitalised at the University of Arkansas for Medical Sciences or the Carraway Methodist Center Inclusion criteria: As above Exclusion criteria: Patients who had received antibiotics in the previous 72 hours; patients with renal failure, pregnancy, lactation, neutropenia or significant penicillin hypersensitivity	Number male/female: I1: 15/27 I2: 24/18 Number black/white: I1: 25/17 I2: 24/18 Mean age (years): I1: 57 I2: 54 Number with underlying disease: I1: 30 I2: 29 The underlying diseases included diabetes mellitus, neoplastic disease, steroid immunosuppression, alcoholism and vascular insufficiency. The prevalence of these per group was not reported Number of type of infection treated I1/I2: Suppurative DFU 10/10 Bacteriologically proven cellulitis 20/17 Culture-negative cellulitis 6/6 Soft tissue abscess 3/6 Suppurative thrombophlebitis 2/0 Suppurative decubitus ulcer 0/2 Gonococcal dermatitis 1/0 Surgical wound infection 0/1 Infections caused by multiple pathogens (includes suppurative diabetic foot and decubitus ulcers and infections related to vascular insufficiency), number of patients in I1/I2: Multiple Gram-negative bacilli and *Staphylococcus aureus* isolated 6/8	I1: Ceftriaxone 1 g given as single daily dose either i.m. in lidocaine 1% suspension or i.v. infused in 100 ml of dextrose 5% in water over 30 minutes (n = 42) I2: Cefazolin 1 g t.d.s. at the University of Arkansas for Medical Sciences and 1 g q.d.s. at the Carraway Methodist Medical Centre, given i.v. infused in 100 ml of dextrose 5% in water over 30 minutes (n = 42)	Statistical methods: Not stated. No p-values were reported. Mean daily dose of cephalosporin used (mg/kg) (all patients): I1: 15.4 I2: 48.5 Number with bacteriological response I1/I2 (DFU patients only): Elimination 6/4 Reduction 3/2 Persistence 1/4 Relapse 0/0 Reinfection 0/0 The above was also reported for other infection types Number of patients with clinical outcomes in I1/I2 with infections caused by multiple pathogens (includes suppurative diabetic foot and decubitus ulcers and infections related to vascular insufficiency): Patients treated (had surgery) 12 (5)/13 (6) Clinical failures (surgery) 0/5(4) Clinical improvement 2/2 Clinical cure (surgery) 10 (5)/6 (2) Number undergoing surgical procedures I1/I2 (all patients): Amputation 7/4 Incision with drainage and debridement 8/8 Some patients had more than one procedure	Three of 6 patients with soft tissue abscess had no bacterial growth on the initial culture and therefore were not included in the bacteriological assessment No withdrawals were reported for the DFU patients	Reviewer's notes: Cultures and sensitivities not reported per type of infection. Most results were not stratified by infection type. Given this and the small proportion of patients with DFU recruited (24%), it is difficult to derive useful outcomes that could be confidently generalised to a wider population with DFU Study sponsorship: Not stated

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
signs of infection) and colonisation (organisms isolated during therapy with no associated clinical signs of infection). For the clinical evaluation, patients were considered cured when there was resolution of signs and symptoms of infection. The number of days required for resolution of fever was recorded daily, as were the clinical signs of drainage and inflammation. Patients were monitored daily for signs of toxicity. Haematological, renal and hepatic parameters were measured every 4 days during therapy and at the end of therapy Setting/length of treatment: Hospital/treatment duration not reported		Group B *streptococci*, Gram-negative bacilli and *Staphylococcus aureus* isolated 6/6 Group A *streptococci*, Gram-negative bacilli and *Staphylococcus aureus* isolated 2/1		Group B streptococci were isolated from the DFUs, but no details provided per group Number with possible cephalosporin-related adverse effects 11/12 (all patients): Eosinophilia 7/5 Thrombocytosis 2/0 Leucopoenia 0/1 Elevated transaminase 2/1 Rash 0/3 Diarrhoea 1/3 The number of days required for resolution of fever, as stated in the methods, was not reported		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Chantelau (1996),[74] Germany Study design: RCT (double-blind) Method of randomisation: Computer-generated code Unit of allocation: Patient Calculation of statistical power: Not reported Outcome assessment: Rate of reduction of ulcer size (surface area calculated by planimetry, transformed into a circle, changes of the circle radius over time were recorded). Frequency of complete healing (standardised photographs). Adverse effects. Compliance with pressure relief (graded as optimal, sufficient, or insufficient, according to clinical judgement). Wounds cultures performed using deep swab, with material placed into transport medium and sealed immediately for determination of aerobic and anaerobic bacteria.	Inclusion criteria: Diabetic patients with polyneuropathy, with skin and soft tissue lesions of the forefoot, age >18 years were included, with foot lesions graded 1A to 2A, according to Wagner and Harkless classification Exclusion criteria: Known hypersensitivity to test medication, antibiotic treatment during the preceding 7 days, bilateral foot lesions, presence of osteomyelitis or peripheral vascular disease, pregnancy, serum creatinine level >130 μmol/1, immune depression due to underlying disease, prior organ transplantation, immunosuppressive drug therapy, microorganisms unresponsive to test medication, inability to comply with protocol	Gender male/female: I: 16/6 C: 12/10 Mean (95% CI) age (year): I: 58 (54 to 62) C: 59 (55 to 63) Mean (95% CI) ulcer area (mm^2): I: 214 (154 to 274) C: 220 (162 to 422) Data were not reported for ulcer grade Mean (95% CI) diabetes duration (year): I: 22 (17 to 27) C: 19 (14 to 24) Insulin dependent: I: 11/22 (50%) C: 12/22 (55%) Number of patients currently smoking: I: 2/22 (9%) C: 5/22 (23%) Number of patients with $HbA1_c$ <8%: I: 9/22 (41%) C: 10/22 (45%) Number of patients with diabetic retinopathy: I: 13/22 (59%) C: 12/22 (55%) Number of patients with proteinuria >500 mg/1: I: 4/22 (18%) C: 2/22 (9%)	I: Amoxycillin 500 mg plus clavulanic acid 125 mg, orally tds (n = 22) C: Identical placebo t.d.s. (n = 22) All patients: Study medication was started within 6 hours of initial wound culture. All received mechanical debridement. The lesion was cleaned with a topical disinfectant (Dibromol solution) and dressed with cotton gauze and paraffinated non-adhering gauze. Pressure relief was provided through the use of a half-shoe, crutches and wheelchairs Outpatient treatment was carried out by a qualified nurse repeating the above wound care procedure daily at the patient's home The study was stopped when the antibiotic proved unsuitable according to baseline cultures (at days 3 or 6), or if no clinical improvement was seen within 6 days or if the study protocol was violated owing to incomplete pressure relief or adverse effects of the medication	Statistical methods: χ^2 and t-tests. At 20 days: Mean (95% CI) reduction in ulcer radius (mm^2day): I: 0.27 (0.15 to 0.39) C: 0.41 (0.21 to 0.61) (ns) Complete healing: I: 6/22 (27%) C: 10/22 (45%) (ns) Adverse effects: One case of diarrhoea in the antibiotic group, which did not require withdrawal Compliance rated as optimal (assessed in 39 patients): I: 16/19 (84%) patients C: 18/20 (90%) patients (ns) Microbiology Number of patients with microbiological findings at entry/day 6/end of study: Gram stains Positive cocci C: 15/6/2 I: 19/9/4 Positive rods C: 1/0/0 I: 5/0/1 Negative rods C: 6/1/2 I: 4/4/1 No microbes C: 0/13/6 I: 0/6/7	I: 3/22 (13.6%) C: 2/22 (9.1%) The above patients were withdrawn within 6 days of the start of the trial owing to non-compliance, or bacteria unresponsive to the antibiotic	Study sponsorship: The authors acknowledged the cooperation of SmithKline-Beecham, Munich, Germany, but it was unclear from this whether the company sponsored the research

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Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Cultures were taken at baseline, day 6 and day 20 in cases of incomplete ulcer healing. Wound assessments and photographs were repeated on days 3, 6, 14 and 20 (or at complete closure of the lesion) Setting and length of treatment: It appears that some patients were treated as inpatients and some as outpatients, but there is no breakdown by numbers. The duration of the trial was 20 days				Isolates *Staphylococcus aureus* C: 5/5/3 I: 9/3/2 *Staphylococcus epidermis* C: 4/3/4 I: 6/1/1 E. coli C: 0/0/1 I: 1/3/0 *Streptococcus B* C: 3/1/0 I: 3/0/0 *Streptococcus faecalis* C: 3/0/0 I: 2/1/0 Others C: 8/3/3 I: 8/5/6 No isolates C: 1/10/1 I: 0/9/4		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
de Lalla (2001),[119] Italy Study design: RCT (1:1) Method of randomisation: Not stated Unit of allocation: Patient Calculation of statistical power: Not reported Outcome assessment: Foot lesions were evaluated by one investigator (blind to randomisation), by recording degree of debridement, condition of granulation tissue, state of ulcer margins, and ulcer width. A photograph of the lesion was taken at each assessment. Microbiological assessment was performed at baseline and at days 7 and 21. Following surgical debridement, scrubbing, and cleansing with sterile gauze soaked in sterile saline, a superficial swab specimen and a deep tissue biopsy were collected from the deep base of the ulcer. Samples were inserted into a transport tube	Population: Adult diabetic patients of either gender admitted to the Diabetes Centre of the San Bortolo Hospital, Vicenza, Italy for severe, limb-threatening foot infection (defined by the presence of full-thickness ulcer, more than 2 cm of cellulitis with or without lymphangitis, bone or joint involvement, or systemic toxicity) Inclusion criteria: As above Exclusion criteria: Treatment with antibiotics for any proven or suspected infection during the 2 weeks preceding recruitment; superficial, non-limb-threatening infection; immediate risk of major above-ankle amputation for critical leg ischaemia (ankle systolic blood pressure <50 mmHg or	Number male/female: C: 14/6 I: 16/4 Mean ± SD (range) age (years): C: 59.8 ± 9.6 (44–85) I: 56.6 ± 8.6 (42–74) Mean ± SD (range) duration of diabetes in years: C: 18.5 ± 8.6 (12–30) I: 15.6 ± 8.6 (1–46) Number (%) of patients with Wagner grade 3/4: C: 14 (70)/6 (30) I: 13 (65)/7 (35) Number (%) of patients with neuropathic/ischaemic/mixed lesions: C: 14 (70) / 0 / 6 (30) I: 13 (65) / 2 (10) / 5 (25) Mean ± SD ankle–brachial blood pressure index: C: 1.29 ± 0.50 I: 0.96 ± 0.34 Mean ± SD vibrator perception threshold: C: 43.2 ± 0.47 I: 35.8 ± 14.60 Number (%) of patients with white cell count >10,000/mm^3: C: 5/20 (25) I: 1/20 (5) Mean ± SD neutrophil count (mm)^3: C: 8300 ± 3500 I: 7800 ± 3500 Number (%) of patients with ESR >70 mm/h: C: 13/20 (65) I: 11/20 (55)	C: Conventional treatment alone (local treatment plus systemic antibiotic therapy) (n = 20) I: Conventional treatment (local treatment plus systemic antibiotic therapy) plus G-CSF 263 μg daily s.c. for 21 days. The dose of G-CSF was temporarily reduced to 175 μg if the neutrophil count exceeded 35,000 cells/mm^3. G-CSF was discontinued if the neutrophil count was over 50,000 cells/mm^3 and was re-commenced only if the count fell to less than 35,000 cells/mm^3 (n = 20) All patients: Local treatment consisted of debridement of soft tissue and bone at enrolment and thereafter of daily inspection, cleansing with sterile water, disinfection with povidone iodine, surgical removal of necrotic tissue as required and occlusive dressing of foot lesions. Empirical antibiotic therapy was based on the combination of ciprofloxacin and clindamycin. I.v. therapy	Statistical methods: One-sample t-test for comparison of continuous variables and Mann–Whitney U-test for categorical variables. Number (%) undergoing amputation at 21 days: C: 5/20 (25) I: 1/20 (5) p = 0.08 Number (%) undergoing amputation at 9-week follow-up: C: 9/20 (45) I: 3/20 (15) p = 0.038 Number undergoing major amputation: C: 2 (at 21 and 30 days) I: 0 Number undergoing amputation of metatarsal bones: C: 1 (at day 25) I: 1 (at day 45) Adverse events: No adverse events associated with G-CSF were observed. Dosage had to be reduced in 2 patients owing to neutrophil count higher than 35,000 cells/mm^3. The neutrophil count did not exceed 50,000 cells/mm^3 in any patient	There were no withdrawals during the 21-day trial or at the 9-week follow-up At 6 months, 4 patients from I were lost to follow-up	Study sponsorship: Not stated

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
containing solid medium suitable for both aerobic and anaerobic microorganisms and delivered to the laboratory for immediate processing. The foot lesions were evaluated at weeks 3 and 9 and classified as one of the following: cure (complete closure of the ulcer without signs of underlying bone infection); improvement (eradication of pathogens indicated by negative swab or tissue culture, coupled with marked or complete reduction of cellulitis but incomplete closure of the ulcer or closure of the ulcer but persistent signs of active underlying bone infection such as local pain, erythema and swelling); or failure (absence of clinical improvement irrespective of culture results). Amputation, defined as any excision of bone segment, was considered failure when its indication was due to persistent infection after 15 days of appropriate antibiotic therapy and local treatment. Indication for amputation	ankle/brachial blood pressure index <0.5); any critical condition with immediate risk of death; renal impairment; history of allergic reaction to ciprofloxacin or clindamycin; any contra-indication to G-CSF administration	Number (%) of patients with positive blood cultures: C: 2/20 (10) I: 0 Detection of osteomyelitis: All patients had osteomyelitis at baseline, detected by positive bone probe. 15 patients (6 in C and 9 in I) had diagnosis confirmed by indium-labelled leukocyte scan combined with technetium-99m bone scan Number (%) of patients with exposed bone: C: 4/20 (20) I: 6/20 (30) Number (%) of patients with life-threatening infection: C: 2/20 (10) I: 0 Mean ± SD number of ulcers per patient: C: 1.4±1.0 I: 1.4±0.6 Number (%) of patients with more than one ulcer: C: 5/20 (25) I: 6/20 (30) Mean ± SD number of isolates per patient: C: 2.30 ± 1.6 I: 2.05 ± 1.2 Number (%) of patients with polymicrobial infection: C: 10/20 (50) I: 14/20 (70)	(ciprofloxacin 400 mg b.i.d. plus clindamycin 900 mg t.i.d.) was administered in the case of more serious infection (febrile disease, extended cellulitis with lymphangitis, incomplete debridement of necrotic tissue, or extensive bone involvement) and the therapy was switched to the oral route when appropriate. The oral regimen (ciprofloxacin at 750 mg b.i.d. plus clindamycin 300 mg q.d.s.) was considered appropriate for less critical patients. Adjustments to treatment were made on the basis of wound cultures and sensitivities Insulin was given either by continuous i.v. infusion or a multiple-dose regimen.	Mean ± SD neutrophil counts (cells/$mm^{3)}$: C: 6,500 ± 4,400 I: 25,200 ± 3,500 $p = 0.002$ Treatment outcomes for number (%) of patients 3 weeks after start of treatment C/I: Cure: 0/0 Improvement: 9 (45)/12 (60) (ns) Failure: 11 (55)/8 (40) (ns) Treatment outcomes for number (%) of patients 9 weeks after start of treatment C/I: Cure: 7 (35)/7 (35) (ns) Improvement: 8 (40)/4 (20) (ns) Failure: 5 (25)/9 (45) (ns) Both patients with life-threatening infection at time of randomisation (both in C) were classified as improved at week 9 Treatment outcomes for number (%) of patients at 6-month follow-up C/I (evaluated in 20 patients in C and 16 in I, as 4 were lost to follow-up): Cure or stable: 15/20 (75)/13/16 (81) Worsened: 5/20 (25)/3/16 (19) ns Number of patients with bacterial isolates C/I after 3 weeks of treatment: Gram-positive aerobes: CNS-MR 3/5 SA-MS 0/1 SA-MR 1/2		

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Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
was assessed by orthopaedic staff at the hospital who were not involved in the study, and had not been blinded to treatment allocation Setting and length of treatment: Hospital. Length of trial 21 days. Follow-up at 9 weeks and 6 months.		Number (%) of patients with cellulitis diameter >2 cm: C: 15/20 (75) I: 10/20 (50) Number (%) of patients with visible infected wet gangrene of the toes: C: 4/20 (20) I: 4/20 (20) Number (%) patients with an abscess: C: 3/20 (15) I: 1/20 (5) Number (%) patients with ulcer diameter >2 cm: C: 11/20 (55) I: 13/20 (65) Number of patients with bacterial isolates C/I: Gram-positive aerobes: CNS-MS 5/1 SA-MS 8/8 SA-MR 2/2 *Corynebacterium* species 2/2 *Enterococcus* species 3/7 *Streptococcus* agalactiae 4/4 *Streptococcus* pyogenes 0/2 Gram-negative aerobes: *Escherichia coli* 1/4 *Proteus mirabilis* 2/0 *Enterobacter aerogenes* 1/0 *Klebsiella pneumoniae* 1/0 Anaerobes: *n* 2/5 *Fusobacterium* species 1/2 *Peptostreptococcus* species 1/4 *Prevotella bivia* 0/1 Total 33 (34%)/41 (55%)		*Corynebacterium* species 1/2 Gram-negative aerobes: *Pseudomonas aeruginosa* 1/1 *Escherichia coli* 2/0 Total 8 (42%)/11 (58%) Mean number of isolates per patient at day 7: C: 1.05 I: 0.95 Mean number of isolates per patient at day 21: C: 0.55 I: 0.55 Number (%) of patients requiring adjustment of empirical antibiotic therapy during the study period: C: 12/20 (60) I: 12/20 (60) Mean ± SD/median (range) duration of antibiotic therapy (days): C: 58.7 ± 23.7/60 (30–119) I: 68.9 ± 29.2/62.5 (30–163) Number (%) of patients undergoing oral/i.v. antibiotic therapy during the study period: C: 11/20 (55)/9/20 (45) I: 13/20 (65)/7/20 (35) ns Vascular reconstruction was not undertaken in any patient during the study period Glucose metabolism was adequately controlled in all patients		

CNS-MR, methicillin-resistant, coagulase negative staphylococci; CNS-MS, methicillin-sensitive, coagulase negative staphylococci; SA-MR, methicillin-resistant, *Staphylococcus aureus*; SA-MS, methicillin-sensitive, *Staphylococcus aureus*.

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Dwivedi (2000),[127] India Study design: RCT Method of randomisation: Not specified Unit of allocation: Patient Calculation of statistical power: Not reported Outcome assessment: Amputation rate Measurement of ulcer margins (centimetre tape by Smelo's device), presence of granulation tissue, absence of purulent discharge (via naked eye examination) histological changes (via tissue biopsies), roentgenogram of affected part, arterial circulation (ultrasound Doppler/AB index), immunological changes (IgG, IgA, IgM via single radial diffusion (Fahey 1965)[331]), total proteins Grading of results by mild, moderate, good recovery Setting and length of treatment: Diabetic clinic/5 years	Inclusion criteria: 100 patients with non-healing diabetic foot ulcer of 6–12 months duration Exclusion criteria: None stated	Gender male/female: 70/30 50 patients each in I1 and I2; gender split not given Age range: 31–70 years Age-matched groups (not stated how done) *Duration of diabetes*: 30% 0–5 years; 40% 6–10 years; 40% >10 years Diabetic control both groups by suitable hypoglycaemic agents or insulin Dietary habit: Both groups 1500–2000 cal per day Social states: 60% rural; 40% urban	I1: 50 patients received suitable systemic antibiotics (according to antibiotic sensitivity) plus metronidazole, local antiseptics and peripheral vascular dilator (Pentoxifylline). I2: 50 patients received a water-soluble solid extract to Manjishtha (*Rubia cordifolia*) and Ashvagandha (*Withania somnifera*) each 500 mg orally, 3 × day. Patients also required to keep affected part dipped in lukewarm decoction of roots of both plants mixed together for 30 minutes daily. Wounds dressed without any conventional local antiseptic Both groups received regular surgical treatment consisting of incision, drainage of abscesses and wound debridement (as and when required) Control group data available for immunoglobulins and total proteins. Values taken from standard readings of age-matched non-diabetics of immunopathology laboratory (Institute of Medical Sciences, Banaras Hindu University)	Results tables available only for immunoglobulins, total proteins and arterial circulation I1: Amputation: 30% of group underwent total or partial amputation (personal communication) (50% in abstract.[127]) IgG levels raised significantly before and after treatment (*t*-value: 0.160; $p < 0.05$). When after treatment compared to control data, *t*-value: 7.32; $p < 0.001$ Patients showed mild to moderate recovery I2: Amputation: 16% of patients underwent partial amputation (personal communication) (20% in abstract.[127]) Statistically significant changes noted in IgG (*t*-value: 0.163; $p < 0.05$), IgA (*t*-value: 1.985; $p < 0.05$), IgM (*t*-value: 1.734; $p < 0.01$) and total protein levels (*t*-value: 0.979; $p < 0.01$) when compared before and after treatment. Compared with control data, only IgG (t value: 7.44; $p < 0.001$), IgA (1.4988; $p < 0.05$) and total protein (0.8785; $p < 0.05$) showed significant improvement Patients showed moderate to good recovery and demonstrable histological changes in reduced subepithelial oedema, reduced exudates, vascular channel	No details	Rationale for defining the study agent as an antimicrobial agent: authors justify effectiveness of Manjishtha on basis of ability of remove microangiopathic and atherosclerotic changes inside the arteries/capillaries in wound area, thus facilitating blood supply, nutrition and removal of microbes. Also that Ashvagandha improved immunological status of patients

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
				profileration and appearance of health granulation tissue. Good improvement in arterial circulation of affected part also noted. Control of purulent discharge (maggots spontaneously discharged after 4–6 dippings) At 3 months: both groups showed statistically significant changes ($p < 0.01$) in ankle brachial pressure index (AB index)		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Erstad (1997),[107] USA Study design: RCT (DB) Method of randomisation: Not stated Unit of allocation: Patient Calculation of statistical power: Not mentioned Outcome assessment: Tissue ischaemia assessed using Doppler-derived ankle–brachial index and palpation of pulses (femoral, popliteal, posterior tibial, and dorsalis pedis). Clinical response classified as: cure (complete resolution of presenting signs and symptoms); improvement (partial improvement of presenting signs and symptoms); failure (no improvement or worsening of presenting signs and symptoms). Patients who required surgery were considered evaluable if the antimicrobial was given for at least 5 days prior to surgery or if the antimicrobial was required postoperatively	Population: Age at least 18 years, with insulin or non-insulin dependent diabetes attending the Vascular Surgery Service at a 300-bed university medical centre in Southern Arizona Inclusion criteria: At least grade I foot infection (see below); not received successful antimicrobial therapy within the previous 4 days, assessed by clinical improvement Exclusion criteria: Known hypersensitivity to penicillins or cephalosporins; creatinine clearance less than 15 ml/minute; recent history of drug or alcohol abuse; concomitant infection at a site other than the foot that required additional antimicrobials; terminal illness; neutropenic;	Gender Not reported Mean (range) age (years): I1: 60.7 (31–77) I2: 57.8 (34–93) Number (%) with type 1/type 2 diabetes: I1: 13/18 (72)/5/18 (28) I2: 12/18 (67)/6/18 (33) Mean duration of diabetes (years): I1: 12.8 I2: 13.3 Number (%) with grade of wound infection I1/I2: Grade I: 2/18 (11%)/1/18 (6%) Grade II: 8/18 (44%)/12/18 (67%) Grade III: 6/18 (33%)/5/18 (28%) Grade IV: 2/18 (11%)/0 The degree of tissue ischaemia as determined by pulse palpation and ankle–brachial index was comparable between the 2 groups (details provided in the paper) Number (%) who had experienced failed outpatient antimicrobial therapy prior to admission: I1: 10/18 (56%) (6 patients received ciprofloxacin) I2: 7/18 (39%) (received a variety of antimicrobial agents) Mean ankle–brachial pressure index of right leg: I1: 0.93 I2: 0.90	I1: A/S 3 g q.d.s. if creatinine clearance more than 50 ml/minute. Same dose was given t.d.s. or b.d. if creatinine clearance 30–50 or 15–30 ml/minute, respectively. Duration of therapy at least 5 days ($n = 18$) I2: Cefoxitin 2 g q.d.s. if creatinine clearance more than 50 ml/minute. Same dose was given t.d.s. or b.d, if creatinine clearance 30–50 or 15–30 ml/minute respectively. Duration of therapy at least 5 days ($n = 18$) All patients: No additional antimicrobials were administered during hospitalisation unless a patient failed to respond to the study antimicrobial therapy within 48 hours, in which case the patient was withdrawn. Surgical interventions were performed as required	Statistical methods: χ^2 test used for clinical and bacteriological evaluations and Wilcoxon rank sum test used to compare groups for mean duration of hospitalisation and mean changes in clinical signs and symptoms from study entry to end of therapy. Fisher's exact test (two-tailed) used to compare the treatment outcomes (successes and failures) of the 2 groups. Analysis was based on intention-to-treat. Number (%) with clinical response to treatment I1/I2: Cured: 1/18 (6)/7/18 (39) Improved: 14/18 (78)/9/18 (50) Failed: 2/18 (11)/1/18 (6) Indeterminate result: 1/18 (6)/1/18 (6) $p = 0.03$ for patients classified as cured, but no significant difference when cure and improvement considered together There was no significant difference between groups in the proportion of patients who had changes in clinical signs and symptoms from baseline to end of therapy Number (%) with bacteriological response to therapy I1/I2: Eradication: 6/6 (100%)/8/11 (73%) Partial eradication: 0/2/11 (18%) Persistence: 0/1/11 (9%)	Number of patients not completing 5-day course of treatment: I1: 1 (due to adverse event unrelated to study medication) I2: 2 (1 due to inadequate response to therapy, 1 due to requirement for concomitant therapy for a vaginal infection) Number of patients evaluable for bacteriological outcome (i.e. culturable material available from infected site at baseline): I1: 6 I2: 11	Reviewer's comment: most, but not all of the patients in this study had a DFU (33/36) The trial authors commented that "the uncontrolled infectious process had often led to loss of foot architecture before hospitalisation and i.v. antimicrobial therapy was indicated to protect against septicaemia before, during and after debridement" Study sponsorship: Not stated

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Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
to control residual signs of infection at the affected site (equating to at least 5 total days of therapy). Patients who were thought not to require an amputation based on the admission investigations, but subsequently required one due to disease progression, were classified as clinical failures. Bacterial eradication (assessed by needle aspiration, or deep tissue or bone sampling during operative debridement) was defined as the disappearance of culturable material or elimination of pathogens at the end of therapy and at 2-week follow-up. If the pathogen was eliminated but a different pathogen emerged during or after therapy, the evaluation was termed eradication/ superinfection. Partial eradication was defined as disappearance of some, but not all of the pathogens. Persistence was defined as presence of initial pathogens at the end of therapy. Indeterminate: results	pregnant; breastfeeding Severity scale for diabetic foot infection used in the trial: Grade I: cellulitis, no skin break Grade II: cellulitis, superficial ulcer and/or puncture wound present Grade III: cellulitis, deep ulcer and/or puncture wound with suspected osteomyelitis Grade IV: cellulitis, deep ulcer, and osteomyelitis with destruction of foot architecture and/or wet gangrene	Mean ankle–brachial pressure index of left leg: I1: 0.90 I2: 0.83		No significant differences were found between groups The overall mean ± SD number of isolates per patient was 3.4±1.1 (not reported per group). At least one species of *Staphylococcus* was isolated from all patients, and all but one patient had at least one species of *Streptococcus* or *Enterococcus*. All of the *Staphylococcus* and *Streptococcus* isolates were susceptible to both study antibiotic regimens, but the *Enterococcus* isolates (25% of patients, all in I1) were susceptible only to A/S. Each patient with isolates susceptible to the prescribed antimicrobial agent had clinical improvement or cure, except for one patient in I1 who required a revascularisation procedure shortly after admission. Of the patients with one or more organisms resistant to the study antimicrobial (25% of patients in each group), all had clinical improvement during therapy Number of patients undergoing amputations I1/I2: Toe only 3/6 Toe and ray 4/1 Below knee 1/1 Number of patients undergoing revascularisation procedures: I1: femorotibial bypass 1 Aortobifemoral bypass and toe amputation 1		

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Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
were those that did not fit into any category for both clinical and bacteriological assessment. Specimens were placed in sterile containers and transported to the laboratory. Specimens were tested for aerobic and anaerobic organisms with subsequent susceptibility testing that included determination of minimum inhibitory concentration of isolates. In addition, the number of isolates identified, surgical procedures required, duration of hospitalisation, and adverse events were recorded Setting/length of treatment: Hospital. Initial follow-up was 2 weeks post-hospital discharge. Later follow-up was 1 year				I2: popliteal–tibial bypass and below-knee amputation 1 Below knee femoropopliteal bypass 1 Iliac angioplasty 1 Popliteal angioplasty 1 Mean (range) duration of hospitalisation (days): I1: 21.1 (6.0–58.0) I2: 12.1 (4.0–39.0) $p = 0.06$ Proportion of patients experiencing gastrointestinal adverse events: I1: 39% I2: 33% Three patients in group I1 suffered a serious adverse event (worsening of congestive cardiac failure) which the authors considered to be unrelated to the study treatment		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Gough (1997),[100] UK Duplicate publication: Gough (1998)[174] Study design: RCT (DB) Method of randomisation: Random number list Unit of allocation: Patient Calculation of statistical power: A sample size of 40 patients was estimated based on evidence of a mean time to resolution of infection of 13.0 (SD 6.5) days in similar patients. A reduction of 6 days was taken as clinically significant with $\alpha = 0.05$ and power of 0.8 Outcomes assessed: Time to hospital discharge (eligibility criteria for discharge were resolution of cellulitis, i.e. disappearance clinically of soft-tissue erythema, no further exudate from the ulcer, skin temperature difference within normal limits, and negative foot ulcer cultures)	Population: Patients admitted from a specialist diabetic foot clinic Inclusion criteria: Adult (>18 years) diabetic patients with extensive cellulitis, defined as an acute spreading infection of the skin with involvement of the subcutaneous tissues, clinically characterised by erythema (>2 cm in diameter) in association with purulent discharge, with or without lymphangitis If a patient had several ulcers, the most severely affected one was studied Exclusion criteria: Absolute neutrophil count of $<1.0 \times 10^9$/l or $>50 \times 10^9$/l; history of malignant disorder; blood dyscrasia; HIV infection; serum creatinine >250 μmol/l or renal replacement therapy; hepatic disease; previous	Number male/female: C: 15/5 I: 14/6 Number white/Afro-Caribbean: C: 15/5 I: 18/2 Median (range) age in (years): C: 66 (58–81) I: 65 (30–86) Median (range) duration of diabetes in (years): C: 19 (1–44) I: 18.5 (0.1–50) Number insulin dependent/non-insulin dependent: C: 4/16 I: 6/14 Number treated with insulin: C: 15 I: 13 Median (range) glycated haemoglobin (%): C: 8.70 (5.5–12.9) I: 9.25 (5.5–13.7) Median (range) body mass index in (kg/m^2): C: 24.9 (21.1–40.7) I: 28.4 (21.0–40.8) Number with nephropathy: C: 5 I: 5 Median (range) vibration perception threshold (volts): C: 37.4 (8.3–50.0) I: 35.7 (18.3–50.0)	I: G-CSF given at an initial dose of 5 μg/k/day, reduced to 2.5 μg/kg/day, if, after 2 doses, the absolute neutrophil count was higher than 25×10^9/l. If the absolute neutrophil count remained above this value after a further 2 doses, 2.5 μg/kg was given on alternate days. If at any point the absolute neutrophil count was $>50 \times 10^9$/l or the total white cell count was $>75 \times 10^9$/l, G-CSF was stopped until the absolute neutrophil count fell below 10×10^9/l. G-CSF was administered as a daily subcutaneous injection for 7 days ($n = 20$) C: Placebo, consisting of a saline solution, identical in appearance with active preparation, administered as a daily subcutaneous injection for 7 days ($n = 20$) All patients: A combination of 4 antibiotics (ceftazidime, amoxicillin, flucloxacillin and metronidazole) was given i.v. until cellulitis and ulcer discharge resolved. Most patients received the following respective doses daily: 3, 1.5, 2 and 1.5 g. Alternatively, vancomycin i.v. was used if there was known penicillin hypersensitivity or if the patient was or had been colonised or	Statistical methods: χ^2 test with Yate's correction for small numbers was used for categorical data, and log-rank test used for time to event data The median (range) dose of G-CSF over the 7 days was 302 (200–440) μg/day, with 9 patients requiring a reduction in dose Number of patients who received antibiotic regimen consisting of ceftazidime, amoxicillin, flucloxacillin, and metronidazole (given i.v. then by mouth if appropriate): C: 15 I: 17 Number of patients who received vancomycin: C: 4 (3 had MRSA, 1 had penicillin allergy) I: 3 (2 had MRSA, 1 had penicillin allergy) Number of patients with evidence of osteomyelitis: C: 12 I: 12 Patients with osteomyelitis received combined oral and i.v. therapy for at least 10 weeks Median (range) time to hospital discharge in days: C: 17.5 (9–100) I: 10 (7–31) $p = 0.02$ Median (range) time to resolution	There were no withdrawals	Authors' note: G-CSF therapy was associated with the development of leucocytosis, due almost entirely to an increase in neutrophil count Normal ranges for haematology analyses, as suggested by trial authors: Total white cells $(4.0–10.0) \times 10^9$/l Neutrophils $(2.5–7.5) \times 10^9$/l Lymphocytes $(1.3–4.0) \times 10^9$/L Monocytes $(0.2–1.5) \times 10^9$/L Rationale for defining the study agent as an antimicrobial agent: Endogenous G-CSF concentrations rise during bacterial sepsis in both neutropenic and non-neutropenic states, suggesting that G-CSF may have a central role in the neutrophil response to

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Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Time to resolution of cellulitis (assessed by skin temperature using infrared thermometer and comparing average of 3 readings within area of cellulitis with those taken from the corresponding site on the non-infected foot, a difference of more than 2°C being defined as abnormal) Time to withdrawal of antibiotics Time to negative swab culture (assessed using daily swabs taken from the deepest part of the wound after cleansing the ulcer with sterile saline and removing superficial debris; specimens were analysed for aerobic and anaerobic culture, and sampling was repeated until cultures were negative on 2 consecutive days) Requirement for surgery Ulcer healing Requirement for angiography and associated procedures Diagnosis of osteomyelitis (using plain radiography and probe	organ transplantation; immunosuppressive therapy including corticosteriods; pregnancy; lactation; multiple organ failure; secondary to septicaemia; critical leg ischaemia (ankle systolic pressure <50 mmHg or ankle/brachial blood pressure index <0.5); dorsal transcutaneous oxygen pressure <30 mmHg Neutrophils from 10 healthy volunteers, matched by age and gender to the diabetic patients, were used as controls for neutrophil function assays	Median (range) Doppler index for ankle/brachial blood pressure ratio: C: 0.99 (0.65–1.50) I: 1.00 (0.53–1.28) Number with retinopathy: C: 13 I: 12 Number receiving antibiotics on recruitment to the trial: C: 3 I: 3 Number currently smoking: C: 2 I: 3 Number with history of coronary or cerebrovascular disease: C: 10 I: 7 Number with previous minor amputation or debridement: C: 13 I: 9 Number with ulcers in the forefoot/midfoot/hindfoot: C: 17/2/1 I: 15/2/2 In addition, one patient in group I had extensive cellulitis secondary to a paronychia without ulceration Number with multiple ulcers: C: 9 I: 7 Median (range) duration of foot ulcer (days): C: 39.5 (2–1825) I: 21.0 (2–1278)	infected during the past year with MRSA. If an infecting pathogen was identified before admission and enrolment, the appropriate antibiotics were used as first-line therapy. Subsequent changes to antibiotic treatment were guided by microbiological cultures and sensitivities. Glycaemic control was optimised with insulin in all participants, using a continuous i.v. infusion or a multiple-dose regimen. Only standard foam dressings were used. All received appropriate podiatric treatment. Decisions about surgical debridement or amputation were based on clinical signs, including the presence of non-viable tissue, the development of gangrene, abscess formation and lack of improvement despite optimum antimicrobial therapy	of cellulitis in days: C: 12 (5–93) I: 7 (5–20) $p = 0.03$ Median (range) time to withdrawal of i.v. antibiotics in (days): C: 14.5 (8–63) I: 8.5 (5–30) $p = 0.02$ Median (range) time to negative swab culture in (days): C: 8 (2–79) (positive swab became sterile in 15 patients) I: 4 (2–10) (positive swab became sterile in 16 patients) $p = 0.02$ Median (range) foot temperature difference in (°C) at day 7: C: 2.1 (0.1–5.8) I: 1.1 (0.1–2.8) $p = 0.011$ Number requiring surgery (debridement under general anaesthesia and/or ray amputation): C: 4 patients (1 during first 7 days, 3 after first 7 days; 2 had toe amputation, 2 had extensive debridement under anaesthesia) I: none $p = 0.114$ Number (%) of patients with resolution of cellulitis at day 7: C: 4 (20%) I: 11 (55%) $p = 0.05$		infection. External administration of G-CSF is thought to increase the release of neutrophils from the bone marrow and improve neutrophil function Study sponsorship: The lead author was supported by a grant from Amgen CA, USA

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Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
to bone) Haematology (samples taken by staff not involved in clinical assessment of the patients; results given to the pharmacist, who undertook changes in doses of G-CSF, which were concealed from the investigators) Effects of G-CSF on the generation of neutrophil superoxide: measured by a spectrophotometric assay Adverse effects Patients were reviewed daily by 3 independent clinicians. All clinical decisions (regarding need for surgery or eligibility for hospital discharge) were made independently of study treatment and white-cell count Setting and length of treatment: Hospital; 7 days		Median (range) duration of cellulitis (days): C: 4 (2–21) I: 5 (1–14) Median (range) foot temperature difference (°C): C: 3.1 (0–9.1) I: 4.3 (1.4–11.2) Median (range) total white cell count ($\times 10^9$/l): C: 7.8 (3.7–11.1) I: 7.6 (4.8–17.1) Median (range) neutrophil count ($\times 10^9$/l): C: 5.5 (1.4–7.9) I: 5.6 (2.6–15.9) Median (range) lymphocyte count ($\times 10^9$/l): C: 1.9 (0.8–3.3) I: 1.8 (0.9–3.3) Median (range) monocyte count ($\times 10^9$/l): C: 0.47 (0.1–1.1) I: 0.39 (0.1–0.9) Microbiology results (number of patients in C/I): Positive wound culture 15/16 Gram-positive aerobes: *Staphylococcus aureus* 5/11 *Streptococcus agalactiae* 0/1 *Streptococcus* C 0/1 *Streptococcus* G 0/2 *Escherichia coli* 3/0 MRSA 3/2		Number (%) of patient with ulcer healed at day 7: C: 0 I: 4 (21%) $p = 0.09$ In patients with multiple ulcers, there was no deterioration in any secondary ulcers Median (range) blood glucose (mmol/l): C: 11.5 (2.7–24.4) I: 12.4 (3.0–27.2) $p = 0.42$ Median (range) insulin dose in (U/kg/day): C: 0.48 (0.15–1.01) I: 0.58 (0.11–1.12) $p = 0.38$ Number of patients undergoing angiography: C: 7 I: 4 $p = 0.5$ Number of patients undergoing percutaneous transluminal balloon angioplasty/vascular surgery/no intervention: C: 3/3/1 – patient refused further intervention I: 2/1/1 – had vascular disease unsuitable for intervention $p = 0.449$ for between-group difference for proportions of patients undergoing angioplasty or surgery There were no significant changes in haemoglobin or in		

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Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
		Gram-negative aerobes: *Enterobacter* species 2/3 *Acinetobacter* species 0/1 *Serratia* species 2/0 *Klebsiella* species 3/0 *Proteus* species 2/0 *Escherichia coli* 2/0 Other 4/1 Anaerobes: *Bacteriodes fragilis* 1/1 Other 2/2 Polymicrobial infection 9/6		platelet counts in either group during the study period Median (range) total white cell count ($\times 10^9$/l) at day 3: C: 6.9 (3.8–11.5) I: 25.8 (17.6–45.5) $p < 0.0001$ Median (range) neutrophil count (x 10^9/l) at day 3: C: 4.5 (2.5–8.5) I: 19.9 (15.5–41.9) $p < 0.0001$ Median (range) lymphocyte count ($\times 10^9$/l) at day 3: C: 1.8 (1.0–2.9) I: 2.3 (0.7–4.5) $p = 0.07$ Median (range) monocyte count ($\times 10^9$/l) at day 3: C: 0.44 (0–1.5) I: 0.48 (0–3.9) $p = 0.201$ Median (range) total white cell count ($\times 10^9$/l) at day 7: C: 6.1 (4.1–12.3) I: 27.8 (10.8–41.0) $p < 0.0001$ Median (range) neutrophil count ($\times 10^9$/l) at day 7: C: 3.8 (1.0–6.7) I: 22.4 (7.9–37.1) $p < 0.0001$ Median (range) lymphocyte count ($\times 10^9$/l) at day 7: C: 1.8 (1.0–5.1) I: 2.6 (1.5–4.9) $p = 0.012$		

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Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
				Median (range) monocyte count ($\times 10^9$/l) at day 7: C: 0.54 (0.2–1.1) I: 0.69 (0.2–3.7) $p = 0.044$ Median (range) neutrophil superoxide production in nmol/10^6 neutrophil in 30 minutes: C: 7.3 (2.1–11.5) I: 16.1 (4.2–24.2) Number of patients with transient rise in serum alkaline phosphatase: C: 1 I: 7 $p < 0.05$ Number of patients with transient bone pain not requiring analgesia: C: not reported I: 3		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Grayson (1994),[44] USA Study design: RCT (DB) Method of randomisation: Computer-generated code Unit of allocation: Patients, but most outcomes are reported in terms of the number of infections per study arm Calculation of statistical power: Assuming recruitment of 40 patients per study arm, it was estimated that, with an expected clinical response rate of 80% for I/C, the power of the study to detect that A/S was not more than 20% less effective than I/C would be 0.7 Outcome assessment: Clinical and microbiological end-points were assessed after 5 days of empirical treatment and at completion of i.v. therapy Blind clinical assessment of signs and symptoms was conducted by 2 physicians daily for the first 6 days, then at regular intervals until the	Population: Diabetic patients with limb-threatening infection of the feet or legs identified by Vascular and Podiatry Services at the New England Deaconess Hospital, Boston, MA, USA Inclusion criteria: Requirement for hospitalisation; age at least 18 years; and presence of diabetes and limb-threatening infection involving the lower extremity. Limb-threatening infection was defined by at least the presence of cellulitis, with or without ulceration or purulent discharge Exclusion criteria: Known hypersensitivity to β-lactam antibiotics; requirement for other concomitant antibiotic treatment; serum creatinine level of 3.5 mg/dl or greater; pregnancy; expected death within 48 hours;	Number male/female: I1: 30/17 I2: 37/9 Mean age (year): I1: 59 I2: 61 Mean duration of diabetes (years): I1: 20 I2: 19 Number (%) of infections with insulin-dependent diabetes: I1: 38 (79) I2: 38 (79) Number (%) of infections with sensory neuropathy: I1: 43 (90) I2: 46 (96) Number (%) of infections with impaired renal function (defined as creatinine level >1.3 mg/dl): I1: 9 (19) I2: 14 (29) Number (%) of infections with temperature of >37.8°C: I1: 21 (44) I2: 13 (27) Number (%) of infections with ulcer present: I1: 42 (92) I2: 46 (96) Number (%) of infections with cellulitis present: I1: 48 (100) I2: 47 (98)	I1: A/S regimen. Usual dose (when creatinine clearance was at least 30 ml/minute) 2 g ampicillin/1 g sulbactam (total 3 g) i.v. q.d.s. In cases of impaired renal function (creatinine clearance 15–29 ml/minute) total dose was reduced to 1.5–3 g b.d. When creatinine clearance was less than 15 ml/minute, the patient was excluded from the study (n = 47 patients with 48 infections) I2: I/C regimen. Usual dose (when creatinine clearance greater than 30 ml/minute) 500 mg i.v. q.d.s. In cases of impaired renal function (creatinine clearance 21–30 ml/minute) dose was reduced to 500 mg t.d.s. When creatinine clearance was 20 ml/minute or less, the patient was excluded from the study (n = 46 patients with 48 infections). All patients: Study medication was commenced within 12 hours of baseline wound cultures. The first 5 days of treatment were defined as a period of empirical therapy as cultures and sensitivities were not available before this time All patients underwent bed rest, surgical drainage and debridement of infected ulcers	Statistical methods: χ^2 test for categorical data; Student's t-test for continuous data Mean ± SD/median (range) number of doses of antibiotic therapy: I1: 47 ± 26/41 (10–121) I2: 55 ± 35/48 (13–178) p = 0.20 Mean ± SD/median (range) duration of antibiotic therapy in days: I1: 13 ± 6.5/12 (4–32) I2: 15 ± 8.6/13 (5–45) p = 0.25 Number of infections with empirical treatment completed (20 doses): I1: 45 I2: 45 Number of infections with significant study violations (missing medication doses): I1: 3 I2: 6 p = 0.48 Number of infections requiring dose reduction: I1: 2 I2: 3 Number of infections where non-protocol i.v. antibiotics were given due to failure of study agent/other reason: I1: 8/3 I2: 6/3	All patients were included in the evaluation at the end of therapy Number (%) of patients lost to follow-up: I1: 8/47 (17) I2: 5/46 (11)	Trial authors' comment: I/C has an antimicrobial activity against a broad spectrum of organisms. A/S has activity similar to, but less broad than, that of I/C Trial authors' comment: in trials of this type there are major differences between evaluations in terms of the role of surgery in treating osteomyelitis as well as the definitions of success and failure. These differences limit the reliability of comparisons of outcome of antibiotic therapy for foot infection in diabetic patients studied in various trials Trial authors' comment: the results cannot be generalised to diabetic patients with a life-threatening

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
completion of therapy. The assessment included documentation of the diameter and depth of ulcers, and the extent of cellulitis, lymphangitis, tissue necrosis and purulent discharge. Daily insulin dosages and surgical procedures were recorded Aerobic and anaerobic cultures of the deep wound (following sharp debridement) or debrided tissue were performed on days 0, 3, 5 and on the final day of i.v. antibiotic treatment. When present, pus was aspirated and submitted for culture in a capped syringe. All identified pathogens were tested for susceptibility to the study drugs The diagnosis of osteomyelitis was made using histopathology, radiology and clinical signs Clinical end-points were: cure (resolution of soft tissue infection); improvement (alleviation of at least 2 presenting signs or symptoms of infection); failure (inadequate	severe underlying disease that might interfere with evaluation of the therapeutic response; immune depression due to underlying disease; prior organ transplantation or immunosuppressive drug therapy; current involvement in a clinical study of an investigational drug; recent treatment failure using antibiotics with similar antimicrobial spectrum to the study agents Creatinine clearance less than 15 ml/min	Number (%) of infections with lymphangitis present: I1: 14 (29) I2: 19 (40) Number (%) of infections with purulent discharge present: I1: 37 (77) I2: 37 (77) Number (%) of infections on forefoot: I1: 44 (92) I2: 43 (90) Number (%) of infections on midfoot: I1: 3 (6) I2: 3 (6) Number (%) of infections on hindfoot: I1: 1 (2) I2: 2 (4) Number (%) of infections with leucocytosis (>10,000 leucocytes/mm^3): I1: 24/48 (50) I2: 27/48 (56) Number (%) of infections with positive blood culture: I1: 2/48 (4) I2: 1/45 (2) Number (%) of infections with osteomyelitis present on plain radiograph: I1: 13/44 (30) I2: 11/44 (25)	and necrotic tissue, vigorous control of diabetes mellitus, and use of sterile wound dressings (gauze soaked in normal saline or one-quarter strength povidone iodine). When appropriate, arterial circulation of the lower limb was evaluated by non-invasive and arteriographic techniques, and surgery was performed as required Antibiotic therapy was revised in cases where the clinical response was unsatisfactory (blinding was maintained). Revision could include use of replacement or additional agents. Following completion of study therapy, patients received a short course of oral antibiotics if necessary Treatment was withdrawn if an urticarial or morbilliform rash developed	Number (%) of infections who underwent surgical debridement only: I1: 9 (19) I2: 15 (31) $p = 0.24$ Number (%) of infections who underwent amputation: I1: 33 (69) I2: 28 (58) $p = 0.25$ Number (%) of amputations involving excision of digits and distal metatarsal bones: I1: 30/33 (91) I2: 27/28 (96) $p = 0.73$ Number (%) of infections who underwent vascular reconstruction: I1: 7 (15) I2: 15 (31) $p = 0.09$ Number with clinical outcome at day 5/end of therapy: Cure: I1: 28/48 (58%)/39/48 (81%) I2: 29/48 (60%)/41/48 (85%) $p = 0.78$ Improvement: I1: 17/48 (35%)/0 I2: 18/48 (38%)/0 Failure: I1: 3/48 (6%)/8/48 (17%) I2: 1/48 (2%)/6/48 (13%) Indeterminate: I1: 0/1/48 (2%) I2: 0/1/48 (2%)		infection as such patients were excluded Study sponsorship: Grant support provided by Pfizer Pharmaceuticals, Roerig Division, New York, USA

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
improvement, necessitating a change in antibiotic therapy); and indeterminate (clinical assessment not possible due to amputation) Microbiological end-points were: eradication (clearance of principal pathogens from the wound; partial eradication (clearance of some but not all pathogens); persistence (persistence of principal pathogens); and superinfection (elimination of principle pathogens but emergence of a new pathogen during treatment) Adverse events were graded as: significant (severe reaction necessitating withdrawal of study agent or specific treatment); moderate/possible (a reaction that did not necessitate withdrawal of study agent or specific treatment); and mild/unlikely (an event uncertainly associated with the study drug) Setting and length of treatment: Hospital, single-centre. Average treatment duration 14 days.		Number (%) of infections with osteomyelitis present on technetium bone scan: I1: 0/2 I2: 1/1 (100) Number (%) of infections with osteomyelitis present on histological assessment of bone: I1: 28/31 (90) I2: 25/32 (78) Number (%) of infections with positive bone culture: I1: 11/12 (97) I2: 7/8 (88) Number (%) of infections with presence of osteomyelitis confirmed by bone histology, bone culture or clinical presence of purulent, non-viable bone: I1: 32/47 (68) I2: 27/48 (56) Number (%) of infections with peripheral vascular disease (defined by diminished or absent pulses): I1: 39 (81) I2: 38 (79) Number of bacterial isolates per group (I1/I2): Gram-positive aerobes: *Staphylococcus aureus* 29/25 Coagulase-negative staphylococci 4/8 *Streptococci* 9/26 *Enterococci* 15/13 Other 2/1 Gram-negative aerobes: *Pseudomonas aeruginosa* 4/3		Number with microbiological outcome at day 5/end of therapy: Eradication: I1: 17/48 (35%)/32/48 (67%) I2: 20/48 (42%)/36/48 (75%) $p = 0.5$ Partial eradication: I1: 18/48 (38%)/8/48 (17%) I2: 15/48 (31%)/5/48 (10%) Persistence: I1: 7/48 (15%)/2/48 (4%) I2: 6/48 (13%)/3/48 (6%) Superinfection: I1: 0 / 2/48 (4%) I2: 0 / 3/48 (6%) Indeterminate: I1: 6/48 (13%)/4/48 (8%) I2: 7/48 (15%)/1/48 (2%) Number (%) of failures of therapy per number of infections in patients with osteomyelitis: I1: 6/32 (19%) I2: 5/27 (19%) Number of failures of therapy per number of episodes associated with resistant pathogens: I1: 7/16 (44%) I2: 4/5 (80%) Number of patients assessable at follow-up: I1: 39 I2: 41 Mean ± SD/median (range) duration of follow-up (weeks): I1: 49 ± 36 / 36 (0-113) I2: 53 ± 35 / 57 (1-108) $p = 0.6$ for means		

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Average duration of follow-up 1 year		Non-*aeruginosa Pseudomonas* species I/0 *Xanthomonas maltophilia* 1/1 *Enterobacter* species 3/6 *Acinetobacter* species 3 / 4 *Morganella* species 2/1 *Serratia* species 3/2 *Klebsiella* species 3/2 *Proteus* species 6/1 *Escherichia coli* 4/2 Other 3/6 Anaerobes: *Bacteroides fragilis* 3/3 Non-*fragilis bacteroides* species 9/15 *Peptococcus* species 3/9 Other 8/6 *Candida* species: 1/2 Number (%) of identified pathogens and their resistance to study agents: Total isolates: I1: 45/48 (94) I2: 47/48 (98) Multiple pathogens: I1: 37/45 (82) I2: 40/47 (85) Gram-positive aerobes alone: I1: 21/45 (47) I2: 14/47 (30) Gram-negative aerobes alone: I1: 0/45 I2: 0/47 Mixed Gram-positive and Gram-negative aerobes alone: I1: 7/45 (9) I2: 11/47 (23) Mixed aerobes and anaerobes: I1: 16/45 (36) I2: 21/47 (45) Anaerobes alone: I1: 1/45 (2)		Number with clinical outcome at follow-up (based on 39 assessable patients in I1 and 41 assessable patients in I2): Cure: I1: 27/39 (69%) I2: 33/41 (80%) Indeterminate: I1: 3/39 (8%) I2: 0/41 Failure: I1: 9/39 (23%) I2: 8/41 (20%) Relapse: I1: 6 I2: 9 Number (%) of adverse events (denominator is number of infections): Significant: I1: 7/48 (15%) I2: 9/48 (19%) Moderate/possible: I1: 8/48 (17%) I2: 6/48 (13%) Mild/unlikely: I1: 1/48 (2%) I2: 2/48 (4%) Total: I1: 16/48 (33%) I2: 17/48 (35%)		

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
		I2: 1/47 (2) Number of isolations of resistant pathogens in 11/12: A/S-resistant aerobes 12/10 Other aerobes with probable resistance 4/5 A/S-resistant anaerobes 0/0 A/S-susceptibility unknown 0/3 I/C-resistant aerobes 2/4 I/C-resistant anaerobes 0/0 I/C-susceptibility unknown 3/2 Number of patients with pathogens potentially resistant to the assigned study drug: 11: 16 I2: 4 Baseline ulcer characteristics such as area or duration were not reported				

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Kastenbauer (2003),[118] Austria Study design: RCT (single-blind: patient blinded) Method of randomisation: Not stated Unit of allocation: Patient Outcome assessment: Resolution of cellulitis, specified clinically and by an infection summary score (ISS). I1: G-CSF (Filgrastim) vs I2: placebo Setting: Inpatients Length of treatment: 10 days	Population: Diabetic patients with infected foot ulcers Inclusion criteria: Diabetic patients with moderate-sized (diameter 0.5–3 cm) infected neuropathic (abnormal 10 g monofilament test) foot ulcer of Wagner's grade 2 or 3 Exclusion criteria: presence of gangrene, haematological diseases, pancytopenia, neoplasia, impaired kidney/liver function, recent treatment with cytokines or immunoactive drugs	$n = 37$ I1 ($n = 20$); I2 ($n = 17$) Male (%): $n = 15$ (75); $n = 12$ (77) Type II Diabetes (%): $n = 19$ (95); $n = 8$ (94) Age (years): 60.8 ± 11.1; 58.2 ± 8.1 Diabetes Duration (years): 14.7 ± 8.5; 15.5 ± 10.6 $HbA1_C$ (%): 8.9 ± 1.7; 9.2 ± 2.6	I1: ($n = 20$) patients received an initial dose of 5 μg/kg body weight G-CSF (Filgrastim: Amgen, Vienna, Austria) injected subcutaneously I2: ($n = 17$) patients received 5 μg/kg body weight placebo (0.9% sterile saline solution) injected s.c. All patients had to maintain strict bed rest and received the same standard of wound care, including debridement. All patients treated with i.v. antibiotics (clindamycin and ciprofloxacin) until inflammation visibly improved. Oral antibiotics administered thereafter if necessary Absolute neutrophil and leukocyte counts measured daily. Treatment was omitted if the absolute neutrophil count was greater than 50,000/l and the absolute leukocyte count greater than 75,000/l, and was re-installed when neutrophils dropped below 30,000 and the leukocyte count below 50,000. Clinical foot inspection: cellulitis (erythema,	Statistical methods: means ± SD; Shapiro–Wilk *W*-test. Mann–Whitney *U*-test, sign test, χ^2 tests. Kaplan-Meier analysis (log-rank test). Primary end-point (by ISS) analysed by ITT and per protocol I1 / I2 Leukocyte count ($\times 10^9$/1): Day 1: 8.1 ± 2.6 / 7.7 ± 1.9 Day 10: 40.8 ± 16.3 / 9.3 ± 8.3 CRP (mg/dl): Day 1: 1.73 ± 2.2 / 1.71 ± 2.31 Days 2–10 (mean): 2.14 ± 2.27 / 1.04 ± 0.63 Wagner grade 1/2/3 (%): Day 1: 0/75/25 / 0/82/18 Day 10: 13/87/0 / 7/93/0 Ulcer volume (μl): Day 1: 203 ± 203 / 358 ± 395 Day 10: 83 ± 140 / 233 ± 235 Proportion of patients achieving complete healing (day 10): I1: 0/20 (0%) I2: 2/17 (11%) Proportion of patients with unresolved cellulitis (day 10): I1: 27% I2: 17% (from survival curve provided by the author) Mean reduction after RX: Absolute: I1: 120 μl I2: 125 μl	Numbers of withdrawals per treatment group: I1: 2 (see adverse events) I2: 1 (osteomyelitis)	Study sponsorship: Amgen, Austria (manufacturers of Filgrastim) The authors describe primary end-point as ISS but this has not been validated as a measure of infection. Healing data were also collected and this is a clinically important outcome

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
			oedema, pus formation and lymphangitis), ISS, ulcer volume, and Wagner's grade carried out daily Presence of erythema (10 points for presence in each section, local, dorsal, lower leg) Lymphangitis (20 points) Difference in circumference: forefoot/ankle/lower leg	Relative (this is biased by the mismatch in ulcer volume at the start of the trial): I1: 120/203 (59%) I2: 125/358 (35%) Adverse events: worsened liver function, skin efflorescence (likely to be attributed to G-CSF) in 2 (I1) patients		

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ISS, infection summary score.

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Lipsky (2004),[109] USA (study population taken from 8 countries: Belgium, Germany, Italy, Portugal, Switzerland, Spain, UK, USA) Study design: RCT (open-label, multicentre – 45 sites) Method of randomisation: Not stated Unit of allocation: Patient Outcome assessment: Clinical cure rate arising from the administration of Linezolid (I1) vs A/C or A/C (I2). Outcome classified as (1) cured, (2) improved or (3) failed Test of cure evaluation conducted 15–21 days after treatment was completed Setting: Inpatient/outpatient Length of treatment: Between 7–28 days	Inclusion criteria: Consenting men and women aged 18 years or over; with diabetes mellitus and a foot infection. Infections defined by clinical signs and symptoms (drainage, erythema, fluctuance, warmth, pain, tenderness, induration) and categorised as one or more of the following: cellulitis, paronychia, infected ulcer, deep soft tissue infection, septic arthritis, abscess, osteomyelitis. Patients could undergo any necessary debridement or other surgical procedures as long as the entire infected area was not resected or amputated Exclusion criteria: Critical ischaemia of the affected limb (defined as absence of pedal pulses, absent or abnormal Doppler waveforms,	371 patients enrolled: 10 received no treatment I1: $n = 241$ I2: $n = 120$ Gender: Male: I1 171 (71%) I2 86 (72%) Female: I1 70 (29%) I2 34 (28%) Ethnicity: White I1 206 (85%) I2 100 (83%) Black I1 27 (11%) I2 16 (13%) Other I1 8 (3%) I2 4 (3%) Mean ± SD age (years) I1 63 ± 12 I2 62 ± 13 Type II diabetes (%) I1 61 I2 52 Type of infection: Infected ulcer I1 190 (79%) I2 93 (78%) Cellulitis I1 101 (42%) I2 60 (50%) Deep soft tissue tissue I1 37 (15%) I2 16 (13%) Paronychia I1 12 (5%) I2 11 (9%) Osteomyelitis I1 57 (24%) I2 20 (17%) Other I1 8 (3%) I2 5 (4%) Foot ischaemia: $n = 98$ (49%) Wound area: "most were ≤2 cm^2 in area" Wound depth: "most were ≤9 mm deep" Wound duration: "most were <8 weeks duration" No data by group to allow comparison	I1: $n = 241$ patients received linezolid (600 mg every 12 hours either i.v. or orally) I2: $n = 120$ patients received A/S (1.5–3 g every 6 hours i.v.) or A/C (500–875 mg every 8–12 hours orally) Therapy given on inpatient or outpatient basis, initiated by either i.v. or oral route and could switch from i.v. to oral at the investigator's discretion. Treatment for at least 7 but for no more than 28 days Vancomycin (1 g every 12 hours i.v., adjusted for renal dysfunction, advanced age or obesity) added to the aminopenicillin/β-lactamase inhibitor regimen if infection with MRSA suspected or confirmed. Investigator could choose to give aztreonam (1–2 g i.v. every 8–12 hours) for patients suspected or documented to have Gram-negative pathogens resistant to study medication	Statistical methods: Intention-to-treat; one-way ANOVA; Wilcoxon rank sum test; χ^2; Fisher's exact test; CIs; frequencies/percentages Definitions of clinical response to treatment: Cured: resolution of all clinical signs and symptoms of infection and a healing wound after ≥5 days of therapy. Improved: resolution of at least two, but not all, clinical signs or symptoms of infection after ≥5 days of therapy (only used at end of treatment). Failed: persistence or progression of baseline clinical signs and symptoms of infection after ≥2 days of therapy. Missing: patients received <2 days of therapy Indeterminate: circumstances precluded classification Clinically evaluable patients (met entry criteria, took 80% of prescribed medication, had adequate follow-up): I1: 203/241 (84%) I2: 103/120 (86%) Overall clinical cure: I1: 165/203 (81%) I2: 77/108 (71%)	I1: 18 I2: 4 Discontinuation due to adverse event	Study sponsorship: Pharamacia Corporation; Department of Veterans Affairs. They describe the ITT population as all people who had received at least one dose of study medication. It should include all who were randomised, regardless of whether they received the study medications Issues worthy of note regarding bioavailability of A/B (i.v./oral) and the potential for early outpatient treatment if a potent, oral agent is available, e.g. fluoroquinolones/ linezolid

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
	toe blood pressure <45 mmHg), unless approved by a vascular surgeon. A wound with prosthetic materials or devices; an infection requiring more than 28 days of antibiotic treatment; a wound with extensive gangrene. Patients also excluded if they had received >72 hours of potentially effective antibiotic therapy in week prior to enrolment; needed additional non-study antibiotic; absolute neutrophil count <500 cells/mm^3; pregnancy or lactating; history of hypersensitivity to linezolid, penicillin or vancomycin		Use of topical antimicrobial agents not permitted Patients received twice-daily dressing changes (any sterile non-adherent type selected by the investigator) and periodic debridement as required. Pressure on the wound avoided by a method selected by the investigator	Results for infected ulcers: (clinical cure) I1: 131/190 (69%) I2: 57/93 (61%) Mean duration of therapy (days ± SD) I1: 17.2 ± 7.9 I2: 16.5 ± 7.9 Clinical cure rates for most frequently isolated baseline pathogens (based on a modified intention-to-treat population, i.e. those patients with a Gram-positive baseline pathogen): I1 (%) I2 (%) *Staphylococcus aureus:* Methicillin sensitive 50/67 (75) 28/39 (72) Methicillin resistant 13/18 (72) 4/7 (57) Coagulase-negative *Staphylococci*: 31/35 (89) 17/19 (90) *Streptococcus agalactiae* 26/31 (84) 9/18 (50) *Enterococcus* spp. 23/34 (68) 13/17 (76) *Pseudomonas* spp. 13/16 (81) 7/11 (64) Enterobacteriacea 52/65 (80) 16/23 (70) Adverse events *n* (%): I1 I2 Any event[a] 64 (26.6) 12 (10) Diarrhoea 18 (7.5) 4 (3.3) Nausea 14 (5.8) 0 (0) Anaemia 11 (4.6) 0 (0) Thrombocytopenia 9 (3.7) 0 (0) Vomiting 4 (1.7) 1 (0.8) Decreased appetite 3 (1.2) 0 (0) Dyspepsia 3 (1.2) 1 (0.8) [a](Statistically significant more events with I1).		

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
				Discontinuation due to adverse event: I1: 18 I2: 4 Use of vancomycin: I1: 1 I2: 5 Use of aztreonam: I1: 12 I2: 3		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Lipsky (unpublished) B,[114] USA Study 304 Full papers not available. Data extracted from abstract presented at 37th ICAAC (Sept. 28–Oct. 1 1997) and CD-Rom slides presented at the FDA Advisory Committee (March 1999) Study design: RCT (double-blind) I1: Pexiganan I2: Ofloxacin Method of randomisation: Not stated Unit of allocation: Patient Calculation of statistical power: Not stated Outcome assessment: Primary: (1) clinical outcome (cured: no further signs or symptoms of infection; improved: significant improvement but incompletely resolved; failed: no apparent response to therapy); (2) microbiological outcome, (3) therapeutic response	Population: 39 centres, 342 (I1 171; I2 171) DFU outpatients Inclusion criteria: Clinical diagnosis of DFU without extensive cellulitis, osteomyelitis, exposure of bone or tendon or fever Exclusion criteria: Osteomyelitis, extensive cellulitis, gangrene, systemic toxicity, inpatient treatment	Gender: (M/F) I1: 118/53 (69/31%) I2: 109/62 (64/36%) Ethnicity: White I1: 142 (83%) I2: 138 (81%) African/American I1: 20 (12%) I2: 24 (14%) Other I1: 9 (5%) I2: 9 (5%) Mean ± SD age (years): I1: 60.8 (11.8) I2: 59.5 (12.4) Treated with oral antidiabetic medication/insulin dependent: I1: Any medication: 170 (99%) Insulin: 118 (69%) Oral agents: 56 (33%) I2: Any medication: 169 (99%) Insulin: 112 (65%) Oral agents: 66 (39%) Body weight mean ± SD (lb): I1: 207.1 (46.0) I2: 209.2 (47.0) Evidence of neuropathy and type: Non-palpable pulses in affected foot: I1 I2 Dorsal pedis: 22 (13%) 17 (10%) Posterial tibial: 29 (17%) 22 (13%) Doppler pulses: 1 (<1%) 2 (<1%) <40 mmHg Neuropathy: I1 I2 Right: 137 (80%) 142 (83%) Left: 40 (82%) 138 (81%)	I1: 171 patients received twice a day application of pexiganan cream (1%) – a broad-spectrum topical antimicrobial agent I2: 171 patients received twice daily dose of ofloxacin (400 mg b.d.) Debridement and off-loading of ulcers performed in addition to antimicrobial therapy. Standard dressings used	Statistical methods: For clinical outcome: Intention-to-treat (ITT): all randomised patients; per-protocol 2 (PP2): ITT patients with none of the nine protocol violations For microbiological outcome and therapeutic response: Intention-to-treat microbiological (ITTM): ITT patients with at least one baseline pathogen; per-protocol microbiological (PP2M): PP2 patients with at least one baseline pathogen Debridement performed: I1 I2 Baseline 93.6 94.2 Day 3 81.9 77.6 Day 10 79.7 75.6 EOT 65.8 63.0 Follow-up 59.8 54.2 Clinical outcome[b] Overall clinical outcome at day 10: I1 I2 95% CI *n/N* % *n/N* % Diff. ITT 152/171 89 151/171 88 –6.16 to 7.33 PP2 96/108 89 106/120 88 –7.71 to 8.82 Overall clinical outcome at end of treatment: I1 I2 95% CI *n/N* % *n/N* % Diff. ITT 153/171 89 153/171 89 –6.51 to 6.51 PP2 98/108 91 109/120 91 –7.62 to 7.44 Overall clinical outcome at follow-up: I1 I2 95% CI *n/N* % *n/N* % Diff. ITT 134/163 82 137/163 84 –9.97 to 6.29 PP2 87/105 83 101/117 86 –13.00 to 6.07	Numbers of withdrawals per treatment group: I1: 16 I2: 15 Reasons for withdrawal: Data not available by study 303/304	Related studies: Lipsky (unpublished B) – see separate data extraction)

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments

Secondary: (1) wound scores and measurements; (2) baseline pathogen eradication

Setting: Outpatients

Length of treatment: 14–28 days

Assessment: Baseline days 3, 10[a], 14, 21, end of treatment (EOT)[a] (14–28 days), follow-up (FU)[a] (2 weeks after end of treatment visit)

[a] Principal time points of interest

Foot ulcer, osteomyelitis and amputation/foot surgery history:

	I1	I2
Foot ulcers	113 (66%)	109 (64%)
Osteomyelitis	34 (20%)	40 (23%)
Amputation/ foot surgery	78 (46%)	64 (37%)
Amputation	49 (29%)	4 9 (29%)

Baseline wound area (median, mm^2) (min.–max.):

I1	I2
146.9 (6.2–2628.0)	160.8 (32.9–1738.0)

Baseline wound depth (median, mm^2) (min.–max.)

I1	I2
3.0 (0–14)	3.0 (0–20)

[b] % response = % cured + % improved
Difference (Diff) = pexiganan % – ofloxacin %

Cured at day 10 (%):

	I1	I2
ITT	20	20
ITTM	19	19
PP2	22	19
PP2M	21	20

Cured at end of treatment (%):

ITT	49	47
ITTM	49	46
PP2	53	51
PP2M	52	51

Cured at follow-up (%):

ITT	51	53
ITTM	51	51
PP2	50	55
PP2M	49	54

Microbiological outcome[c]

Overall microbiological outcome at day 10:

	I1		I2		95% CI
	n/N	%	*n/N*	%	Diff.
ITTM	44/138	32	30/140	21	0.12 to 20.79
PP2M	31/89	35	20/96	21	1.18 to 26.81

Overall microbiological outcome at end of treatment:

	I1		I2		95% CI
	n/N	%	*n/N*	%	Diff.
ITTM	63/138	46	66/140	47	–13.22 to 10.24
PP2M	45/89	51	50/96	52	–15.95 to 12.90

Overall microbiological outcome at follow-up:

	I1		I2		95% CI
	n/N	%	*n/N*	%	Diff.
TTM	63/138	46	66/140	47	–13.22 to 10.24
PP2M	45/89	51	50/96	52	–15.95 to 12.90

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments

[c] % response = % resolved + %improved
Diff. = pexiganan% – ofloxacin%

Microbiological outcome 'resolved' at end of treatment:

	I1	I2
ITTM	53 (38%)	59 (42%)

Microbiological outcome 'resolved' at follow-up:

	I1	I2
ITTM	50 (38%)	61 (46%)

Therapeutic response[d]

Therapeutic response at end of treatment:

	I1		I2		95% CI
	n/*N*	%	*n*/*N*	%	Diff.
ITTM	46/138	38	53/140	38	–15.77 to 6.73
PP2M	32/89	36	36/96	41	–18.68 to 9.34

Therapeutic response at follow-up:

	I1		I2		95% CI
	n/*N*	%	*n*/*N*	%	Diff.
ITTM	48/130	37	60/134	45	–19.68 to 3.97
PP2M	32/86	37	44/94	47	–23.97 to 4.77

[d] % response = % clinically cured + microbiologically resolved
Difference = pexiganan % – ofloxacin %
Reduction in wound area (mm^2) from baseline by EOT (FU) clinical response (ITT):

	EOT		FU	
	I1	I2	I1	I2
Cured:				
Median	–72.8	–113.6	–91.8	–123.7
Mean	–90.3	–183.6	–109.2	–184.4
Median (%)	–67.1	–77.8	–78.9	–93.9
Mean (%)	–56.0	–65.8	–57.1	–76.5
Improved:				
Median	–69.4	–69.2	–60.7	–60.5
Mean	–120.6	–80.9	–98.6	–109.6

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments

Median (%) –46.5 –45.1 –37.9 –38.8
Mean (%) –38.8 –35.7 –14.3 –32.6

Failed:
Median 22.1 –38.3 –0.9 –44.3
Mean 39.9 –83.4 24.4 –90.0
Median (%) 10.8 –20.8 –1.3 –49.4
Mean (%) 21.0 –18.3 19.9 –22.7

Most frequent baseline pathogens eradicated at follow-up (ITTM):

	I1		I2	
	n/N	%	*n*/N	%
Staphylococcus aureus	29/55	53	42/70	60
Enterococcus faecalis	25/49	51	32/47	68
Streptococcus agalactiae	13/25	52	13/23	57
Staphylococcus epidermis	8/13	62	7/11	64
Pseudomonas aeruginosa	7/11	64	11/16	69
Enterococcus species	4/9	44	1/4	25
Streptococcus canis	3/9	33	5/10	50
Escherichia coli	7/7	100	7/8	88
Prevotella bivia	7/7	100	4/4	100
Proteus mirablis	3/7	43	6/10	60

Amputation (incidence and type, e.g. major/minor)
I1: 7
I2: 3

Number/duration of hospital admissions for DFU problems (by EOT and FU failures):

	EOT failures	FU failures
I1:	3	4
I2:	6	7

Adverse events leading to patient withdrawal:

	I1		I2	
	n	%	*n*	%
At least one adverse event leading to withdrawal	16	9	15	9

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
				Most frequent adverse event (combined studies 303/304): Diarrhoea Nausea Pain Serious adverse events: I1: 22 (13%) I2: 19 (11%)		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Lipsky (unpublished) A,[114] USA Study 303 Full papers not available. Data extracted from abstract presented at 37th ICAAC (Sept. 28–Oct. 1, 1997) and CD-Rom slides presented at the FDA Advisory Committee (March 1999) Study design: RCT (double-blind) I1: Pexiganan I2: Ofloxacin Method of randomisation: Not stated Unit of allocation: Patient Calculation of statistical power: Not stated Outcome assessment: Primary: (1) clinical outcome (cured: no further signs or symptoms of infection; improved: significant improvement but incompletely resolved; failed: no apparent response to therapy); (2) microbiological outcome; (3) therapeutic response	Population: 42 centers, 493 (I1 247; I2 246) DFU outpatients Inclusion criteria: Clinical diagnosis of diabetic foot ulcer without extensive cellulitis, osteomyelitis, exposure of bone or tendon or fever Exclusion criteria: Osteomyelitis, extensive cellulitis, gangrene, systemic toxicity, inpatient treatment	Gender: (M/F) I1: 185/62 (75/25%) I2: 180/66 (73/27%) Ethnicity: White I1: 184 (74%); I2: 192 (78%) African/American I1: 22 (9%); I2: 20 (8%) Other I1: 41 (17%); I2: 34 (14%) Mean ± SD age (years): I1: 58.3 (12.2) I2: 58.7 (12.1) Treated with oral antidiabetic medication/insulin dependent: I1: Any medication: 246 (100%); Insulin: 171 (69%); Oral agents: 82 (33%) I2: Any medication: 243 (99%); Insulin: 151 (61%); Oral agents: 97 (39%) Body weight mean ± SD (lb): I1: 207.8 (48.5) I2: 211.3 (44.7) Evidence of neuropathy, and type: Non-palpable pulses in affected foot: Dorsal pedis: I1 23 (9%); I2 24 (10%) Posterial tibial: I1 31 (13%); I2 30 (12%) Doppler pulses: I1 5 (2%); I2 3 (1%) <40 mmHg Neuropathy: Right: I1 214 (87%); I2 216 (88%) Left: I1 219 (89%); I2 213 (87%)	I1: 247 patients received twice a day application of pexiganan cream (1%) – a broad-spectrum topical antimicrobial agent I2: 246 patients received twice daily dose of ofloxacin (400 mg b.d.) Debridement and off-loading of ulcers performed in addition to antimicrobial therapy. Standard dressings used	Statistical methods: For clinical outcome: Intention-to-treat (ITT): all randomised patients; per protocol 2 (PP2) (judged to have completed at least 75% of doses): ITT patients with none of the nine protocol violations For microbiological outcome and therapeutic response: Intention-to-treat microbiological (ITTM): ITT patients with at least one baseline pathogen; per protocol microbiological (PP2M): PP2 patients with at least one baseline pathogen Debridement performed (ITT): Baseline I1 96.8; I2 93.1 Day 3 I1 82.5; I2 79.7 Day 10 I1 86.1; I2 83.9 End of treatment I1 71.7; I2 63.9 Follow-up I1 68.4; I2 63.1 Clinical outcome[b] Overall clinical outcome at day 10: ITT I1 208/247 84; I2 220/246 89; 95% CI Diff. –11.18 to 0.74 PP2 I1 105/125 84; I2 127/141 90; 95% CI Diff. –14.18 to 2.04 Overall clinical outcome at end of treatment: ITT I1 210/247 85; I2 224/246 91; 95% CI Diff. –11.74 to –0.33 PP2 I1 106/125 85; I2 129/141 91; 95% CI Diff. –14.50 to 1.12 Overall clinical outcome at follow-up: ITT I1 186/243 77; I2 201/240 84; 95% CI Diff. –14.29 to –0.12 PP2 I1 92/123 75; I2 118/140 84; 95% CI Diff. –19.25 to 0.28	Numbers of withdrawals per treatment group: I1: 28 I2: 23 Reasons for withdrawal: Data not available by study 303/304 Overall: Cellulitis I1 15; I2 7 Infection I1 4; I2 4 OsteoM I1 4; I2 3 1+ AE I1 44; I2 38	Related studies: Lipsky *et al.* (unpublished) A see separate data extraction)

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments

Secondary: (1) wound scores and measurements, (2) baseline pathogen eradication

Setting: Outpatients

Length of treatment: 14–28 days
Assessment: Baseline, days 3, 10[a], 14, 21, end of treatment (EOT)[a] (14–28 days), Follow-up (FU)[a] (2 weeks after end of treatment visit)

[a] Principal time points of interest

Foot ulcer, osteomyelitis and amputation/foot surgery history:

	I1	I2
Foot ulcers	164 (66%)	145 (59%)
Osteomyelitis	80 (32%)	59 (24%)
Amputation/ foot surgery	121 (49%)	85 (35%)
Amputation	94 (38%)	64 (26%)

Baseline wound area (median mm^2): (min–max.)

I1	I2
131.5 (0–2237.0)	117.3 (6.2–1991.0)

Baseline wound depth (median mm) (min.–max.)

I1	I2
3.0 (0.1–13)	3.0 (0–14)

[b] % response = % cured + % improved
Difference = pexiganan % – ofloxacin %

Cured at day 10 (%):

	I1	I2
ITT	26	28
ITTM	22	26
PP2	24	28
PP2M	22	24

Cured at end of treatment (%):

ITT	54	61
ITTM	52	56
PP2	53	62
PP2M	55	55

Cured at follow-up (%):

ITT	56	65
ITTM	55	60
PP2	56	63
PP2M	55	59

Microbiological outcome[c]

Overall microbiological outcome at day 10:

	I1		I2		95% CI
	n/N	%	*n/N*	%	Diff.
ITTM	73/189	39	66/198	33	–4.27 to 14.85
PP2M	40/95	42	45/121	37	–8.24 to 18.07

Overall microbiological outcome at end of treatment:

	I1		I2		95% CI
	n/N	%	*n/N*	%	Diff.
ITTM	91/189	48	94/198	47	–9.29 to 10.63
PP2M	50/95	53	58/121	48	–8.73 to 18.13

Overall microbiological outcome at follow-up:

	I1		I2		95% CI
	n/N	%	*n/N*	%	Diff.
ITTM	78/185	42	90/194	46	–14.23 to 5.77
PP2M	42/93	45	55/121	45	–13.76 to 13.17

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments

[c] % response = % resolved + % improved
Diff. = pexiganan % – ofloxacin %

Microbiological outcome 'resolved' at end of treatment:

	I1	I2
ITTM	74 (39%)	82 (41%)

Microbiological 'resolved' at follow-up:

ITTM	75 (41%)	84 (43%)

Therapeutic response[d]

Therapeutic response at end of treatment:

	I1		I2		95% CI
	n/N	%	*n/N*	%	Diff.
ITTM	67/189	35	75/198	38	–12.03 to 7.18
PP2M	38/95	40	48/121	40	–12.83 to 13.49

Therapeutic response at follow-up:

	I1		I2		95% CI
	n/N	%	*n/N*	%	Diff.
ITTM	73/185	39	82/193	42	–12.94 to 6.89
PP2M	38/93	41	50/120	42	–14.14 to 12.53

[d] % response = % clinically cured + microbiologically resolved
Diff. = pexiganan % – ofloxacin %

Reduction in wound area (mm^2) from baseline by EOT (FU) clinical response (ITT):

	EOT		FU	
	I1	I2	I1	I2
Cured:				
Median	–67.7	–64.6	–74.9	–69.2
Mean	–123.2	–99.6	–120.0	–114.4
Median (%)	–75.2	–76.5	–84.6	–87.1
Mean (%)	–62.8	–63.2	–62.0	–68.9
Improved:				
Median	–54.3	–47.9	–51.8	–50.9
Mean	–70.2	–81.3	–86.2	–87.9
Median(%)	–35.7	–37.8	–26.1	–35.2
Mean(%)	–29.6	–25.2	–30.9	–28.4

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments

Failed:

Median	2.6	–30.1	–43.1	–59.7
Mean	36.4	–117.8	–33.8	–168.3
Median(%)	0.9	–24.1	–29.7	–27.2
Mean(%)	21.3	–19.0	–13.4	–30.2

Most frequent baseline pathogens eradicated at follow-up (ITTM):

	I1		I2	
	n/*N*	%	*n*/*N*	%
Staphylococcus aureus	43/87	49	55/91	60
Enterococcus faecalis	33/56	59	35/58	60
Streptococcus agalactiae	18/34	53	26/43	60
Enterococcus species	12/17	71	6/8	75
Proteus mirablis	9/13	69	9/11	82
Streptococcus species	11/13	85	6/9	67
Echerichia coli	8/12	67	7/8	88
Pseudomonas aeruginosa	4/11	36	10/20	50
Staphylococcus epidermidis	7/11	64	9/12	75

Amputation:
I1: 4
I2: 6

Number/duration of hospital admissions for DFU problems (by EOT and FU failures):

	EOT failures	FU failures
I1:	11	14
I2:	4	9

Adverse events leading to patient withdrawal:

	I1		I2	
	n	%	*n*	%
At least one adverse event leading to withdrawal	28	11	23	9

Most frequent adverse event (combined studies 303/304):

	I1	I2
Diarrhoea	4	2
Nausea	2	2
Pain	2	1

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results		Withdrawals	Comments
				Probably related adverse events:			
				418	417		
				Serious adverse events:			
				(*n* = 28)	(*n* = 20)		
				11%	8%		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Lipsky (1990),[75] USA Study design: RCT Method of randomisation: Not specified Unit of allocation: Patient Calculation of statistical power: See Comments section Outcome assessment (blinded): Wound healing/size of ulcer (clinical classification); pathogen profile (microbiological classification) Setting and length of treatment: Outpatient clinic/2 weeks (+ 3 months follow-up) Recruitment: October 1985–March 1988 Written informed consent: Local Committee ethical approval	Population: Diabetic outpatients – Seattle (WA) Veterans Affairs Medical Center Inclusion criteria: Patients with clinically infected lesion (lower extremity). No antimicrobial therapy preceding 2 weeks (lesions were ± break in skin) Exclusion criteria: Presence of systemic toxicity (e.g. high fever, hypotension), presence of immediate life or limb threat, inability to perform daily wound care, history of patient non-compliance with outpatient treatment, unwillingness to return for outpatient visits, allergy to study drugs Definition of infection: recent development of	All male (n = 60) I1: n = 27 I2: n = 29 Mean ± SEM age (years): I1: 59.4 ± 2.3 I2: 62.7 ± 2.4 Non-insulin-dependent diabetes: I1: 23 (85%) I2: 28 (97%) Insulin-treated: I1: 19 (70%) I2: 18 (62%) Lesion ulcerated: I1: 24 (89%) I2: 27 (93%) Infection present <1 month: I1: 26 (96%) I2: 28 (97%) Lesion foul smelling: I1: 2 (7%) I2: 2 (7%) Anaerobes isolated: I1: 4 (15%) I2: 3 (10%) Aerobic Gram-negative bacilli isolated: I1: 7 (26%) I2: 5 (17%) No use of antimicrobial agents in preceding 2 weeks Authors report no statistically significant differences between groups on demographic, clinical or microbiological characteristics 60 patients randomised, but data on	I1: n = 27 received oral clindamycin hydrochloride (Cleocin) 300 mg, 4× daily for 2 weeks I2: n = 29 received oral cephalexin (Keflex) 500 mg, 4× daily for 2 weeks Patients were seen in outpatient clinic every 3–7 days, depending on severity of infection Wound care: All lesions cleansed, dressed and debridement administered (where necessary) at initial evaluation. Patients advised to perform twice-daily cleansing and dressing regimen, avoid unnecessary ambulation, self-evaluation/call research nurse if necessary Those whose infections failed to improve, or worsened, were withdrawn from the study and hospitalised. Those whose cultures yielded one or more isolates resistant to the study antibiotic were assessed. Therapy continued if infection improving, otherwise other appropriate treatment	Infection response: (n = 56) I1 / I2 Cured: 21 (78%) / 21 (72%) Improved: 5 (19%) / 4 (14%) Failed: 1 (4%) / 4 (14%) Bacteriological response: (n = 52) I1 (n = 26) / I2 (n = 26) Cured: 20 (77%) / 20 (77%) Improved: 4 (15%) / 2 (8%) Failed: 2 (8%) / 2 (8%) Superinfection: 3 (12%) / 1 (4%) Wound healing: (n = 52) I1 (n = 25) / I2 (n=27) Healed: 10 (40%) / 9 (33%) Progress: 14 (56%) / 18 (67%) Unimproved: 1 (4%) / 0 (0%) Recurrence at follow-up (15 ± 9 months): 8/51 (16%) of patients with cured or improved infection at 2 weeks required therapy for subsequent infection at same site 4 patients required treatment (>2 weeks) (I2) Acquisition of resistant organisms: noted in 1 patient (I1) and 4 patients (I2) Adverse events: I1:1 patient with mild diarrhoea – resolved I2:2 patients with mild nausea and diarrhoea – resolved	Numbers of withdrawals: 2 Reasons for withdrawal: hospitalisation (1 was due to reasons unrelated to the infection) Query these as 'withdrawals' – there was no criteria for defining a withdrawal	Limitations of the study (as noted by authors): Difference in overall infection response rate between I1 and I2 was not statistically significant due to low power All male Study sponsorship: Authors acknowledge 'grant-in-aid' from Upjohn, Kalamazoo, MI, USA Definition of outcomes: Cured = all signs and symptoms of infection had resolved Improved = most signs and symptoms had resolved Failed = no substantial

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
	purulence *or* at least 2 of the following: erythema, warmth, tenderness, induration, fluctuance, drainage	56 reported as 4 were excluded as: detection of osteomyelitis after randomisation (n = 2); patient insistence on being hospitalised (n = 1); patient failure to take A/B (n = 1)	administered. After 2 weeks of therapy, those showing improvement but persisting clinical signs of infection were instructed to continue prescribed regimen. On each return visit, medication compliance reviewed and adverse drug effects assessed Local care of ulcers included coverage with fine mesh, non-adherent dressing and dry gauze on top of that. Cleansing of ulcer (by patient) was with hydrogen peroxide (twice/daily)			improvement in infection AND a change in A/B treatment OR surgical intervention believed necessary

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Marchina (1997),[123] Italy Study design: RCT (single-blind) Method of randomisation: Not stated Unit of allocation: Patients Calculation of statistical power: No *a priori* power calculation reported Outcome assessment: Healing progress assessed at 5, 10 and 15 days. Wounds were graded as one of the following: 3: complete healing 2: >50% wound area healed, relative to baseline 1: 25–50% healed Unsatisfactory <25% healed No information given about methods of measurement or how many assessors involved Treatment duration: 15-day trial. Setting not stated	Inclusion criteria: Patients aged 65 years and over, with DFUs, venous leg ulcers and pressure sores. Wounds had to be classified as 1st or 2nd degree (not defined) Exclusion criteria: Sensitivity to test medication, receiving other treatment	Gender (M/F): I 6/14 C 8/12 Mean ± SD (range) age (years): I 76.7 ± 5.2 (66–86) C 79.1 ± 6.4 (67–89) Wound type: Pressure ulcer/diabetic foot I 9/11 C 10/10 Wound condition: Good/moderate/poor Pressure ulcers I 0/3/6 C 0/3/7 DFUs I 4/6/1 C 3/7/0 No information given on baseline wound area 38 patients presented other co-morbidities (e.g. diabetes mellitus, hypertension) and continued with usual medication during the study period	I: Wounds were cleaned with normal saline and dried with gauze. An antiseptic spray (2% eosin and 0.3% chloroxylenol in hydroglycolic solution) was applied to the wound surface using gauze. Wound was then covered with gauze. The dressing was changed 2–3 times per day. There were no details of the use of other interventions (e.g. pressure relief) Patients who were being treated with an antiseptic prior to the study had a 1 day 'wash-out' period, during which the wound was cleaned 2–3 times with normal saline. During the study period, treatment with other antiseptics, healing medications, antibiotics, analgesics, absorbing agents and anti-inflammatory agents was discontinued. (n = 20) C: As above, except that an alternative spray was used (not described). (n = 20)	At 15 days Healing (3/2/1/unsatisfactory) All wounds I 58%/12%/30%/0 C 30%/40%/18%/12% Figures taken from graph Healing (3/2/1/unsatisfactory) For DFUs only I 82%/18%/0/0 C 50%/50%/0/0 Figures taken from graph Healing (3/2/1/unsatisfactory) For pressure ulcers only I 20%/10%/70%/0 C 10%/30%/30%/30% Figures taken from graph Adverse effects (local burning sensation) I 3 patients C 1 patient	No withdrawals	This is a small study. Larger numbers may be required to detect the true treatment effect The baseline and end-point assessments of wound condition appear to be based on a subjective assessment. There are no details of independent assessments by more than one examiner, and blinding procedures are also unclear. The reliability of the results may therefore be questionable

C, control group; I, intervention group.

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Markevich (2000),[105] Ukraine RCT Method of randomisation Not stated Unit of allocation: Patient No presentation of power calculation Outcome assessment: Number of ulcers healed, proportion of ulcers with at least 50% granulation tissue, proportion of patients with at least 50% reduction in wound area, wound depth and volume, evaluation of surrounding skin, tissue quality (necrotic, slough, fibrotic or granulation), exudate, odour and glucose levels Setting: Inpatients in Lviv Medical University Hospital	Population: 140 people with neuropathic foot wounds requiring debridement Inclusion criteria: None stated in short abstract but another conference report states diabetes mellitus, neuropathy, grade 2 or 3 ulcers with slough, palpable foot pulses Exclusion criteria: None stated in short abstract but another conference report states peripheral vascular disease, ischaemic heart disease, renal failure, hepatic disease, rheumatoid arthritis, immuno-compromised and concurrent steroid therapy	Mean age: 53.6 years (±15.4 years) (unclear what figure ± represents) Mean duration of diabetes: 15.8 ±10.7 years (unclear if ± is SD/SE or range) Mean ± SD ulcer area: I1: Larval therapy group – 14.9 cm^2 I2: Hydrogel group – 15.14 cm^2 Authors state: "wound surface area, depth and volume, evaluation of surrounding skin, tissue quality (necrotic, slough, fibrotic or granulation) and healing rates, exudate, odour and glucose levels were comparable at baseline" but no data provided other than on wound area No data on gender, ethnicity or type of diabetes for all 140 participants, but data available for 22 patients reported at a conference: Male/female: 45%/55% Type I/II diabetes: 27%/73% Ulcer grade 2/3: 86%/14%	I1: Larval therapy (sterile larvae of the green bottle fly, *Lucilia serricata*) 6–10 larvae per 1 cm^2 wound area, removed after 72 hours. Dressings lying above larvae were changed as required. Up to three applications of larvae were used. $n = 70$ I2: Hydrogel dressing (unnamed). Dressing removed at least every three days. $n = 70$ No information on concurrent treatments (such as bed rest). All participants were hospital inpatients	Statistical methods: 3-way ANOVA, independent *t*-test, χ^2 test Proportion of patients achieving complete healing in 10 days: I1: 5/70 (7.1%) I2: 2/70 (2.9%) Proportion of patients with at least 50% granulation tissue in wound: I1: 60% (?42/70) I2: 34.3% (?24/70) $p < 0.001$ Proportion of patients with at least 50% reduction in area of wound: I1. 51.1% (?36/70) I2. 27.1% (?19/70) $p < 0.05$	Numbers of withdrawals per treatment group: not stated	Abstract available on full study ($n = 140$), but presentation of results from 52 patients (? an interim analysis) obtained from conference proceedings No information on funding/sponsorship 10-day follow-up is too short to capture ulcer healing The report does not report the proportion of people whose ulcer became completely debrided in the 10-day period in the two groups, the number of larval therapy treatments required or the median time to complete debridement The ulcers in this study are large (area of 15 cm^2) in comparison with other DFU studies and this may affect its generalisability

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Peterson (1989),[101] USA Study design: RCT Method of randomisation: Pharmacy Service randomly assigned patients ciprofloxacin at a dose of either 750 or 1000 mg orally twice daily. All others were blinded to the randomisation by the use of placebo to make the number of daily doses identical in both groups Unit of allocation: Patient Outcome assessment: Response to two different doses of ciprofloxacin (I1, 750 mg twice daily; I2, 1000 mg twice daily): fully successful outcome defined as not requiring either repeat antimicrobial therapy for initial infection or amputation of the involved extremity	Population: Adults with peripheral vascular disease (but unclear whether wounds are diabetic or vascular in origin) Inclusion criteria: (1) History of clinical evidence of peripheral vascular disease or diabetes mellitus; (2) purulent-appearing lower extremity lesion of sufficient severity to require hospitalisation for intravenous antimicrobial therapy; (3) had two or more signs of infection including local heat, oedema, drainage, erythema, pain, or temperature greater than 37.8°C	48 patients Gender: M 47, F 1 Mean ± SD age: 64 years No. with diabetes mellitus: 46/48 (96%) No. with osteomyelitis: 31/48 (65%) No. with cellulitis: 16/48 (33%)	I1: (n= 24) received ciprofloxacin at 750 mg orally twice daily. Patients diagnosed as having osteomyelitis when compatible changes were observed, either radiographically or on three-phase bone scan. These patients given 3 months of therapy. Patients who had no evidence of osteomyelitis were given 3 weeks of treatment. No other antimicrobials were given to patients (concurrently or following ciprofloxacin therapy) unless it was determined that the quinolone treatment was a failure I2 (n = 24): As above, but 1000 mg oral ciprofloxacin given twice daily Local wound care: both groups. (1) debridement of wound to remove surface eschars and necrotic material; (2) maintenance of a clean wound by foot soaking and wet or dry gauze dressings; (3) avoidance of any pressure on the wound itself; (4) therapy of the infected lesion with systemic rather than topical antimicrobial agents	Fully evaluable patients: I1: 23 patients I2: 22 patients Amputation: (in those for whom therapy failed) I1: 6/11 (55%) I2: 3/7 (43%) Long-term outcome (defined earlier) in patients treated for (a) osteomyelitis and (b) cellulitis (%): Total (a) 19 (65); (b) 8 (50) I1: (a) 10 (67), (b) 2 (25) I2: (a) 9 (64), (b) 6 (75) Adverse events: I2: 2 patients required cessation of treatment. One was due to nausea and vomiting, which began following hospital discharge at 2 days. The other patient discontinued at 34 days due to severe anxiety, similar to that previously experienced with other medications 6 patients (I2), 2 patients (I1) experienced chemical abnormalities (increased blood urea nitrogen or serum creatinine levels)	Numbers of withdrawals (although withdrawal not defined) per treatment group: I1: 1 received amputation within 24 hours of enrolment I2: 2 patients due to adverse events (see previous note)	Study sponsorship: Miles Pharmaceuticals, West Haven, CT, USA

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Setting and length of treatment: inpatients at the Minneapolis Veterans Administration Medical Center. Treatment over 72 hours/follow-up at 12 months	Exclusion criteria: (1) Failure to give informed consent; (2) allergy to quinolone antibiotics; (3) prior antibiotic therapy given within the previous 72 hours that was effective, *in vivo* or *in vitro*, against their pathogenic bacterial isolates. No patient was excluded for the first two indications		Swab cultures obtained after the surface of the wound has been thoroughly cleansed to minimise surface contamination			

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Rhaiem (1998),[124] Tunisia Study design: RCT Method of randomisation: Not stated Unit of allocation: Patient Calculation of statistical power: Not described Outcome assessment: The main outcomes reported per study group were healing rate and time to healing. Where healing rates were reported according to socio-economic level, a score was calculated according to the following: level of education (0 illiterate, 1 primary school level, 2 secondary school, 3 further education); profession (0 unemployed, 1 low income, 2 moderate income, 3 high income); type of housing and number of dependants Setting and length of treatment: Hospital; mean±sd (?) length of hospital stay: 40±13 days	Population: Diabetic patients with cutaneous wounds, hospitalised at Rabta Hospital, Tunisia, between 1992 and 1995 Inclusion criteria: As above Exclusion criteria: Not stated	Baseline characteristics were reported for the sample overall, and not per study group Number male/female: 59/21 Mean ± SD (?) (range) age (years): 56 ± 32 (26–89) Number with insulin-dependent/non-insulin dependent diabetes: 61/19 Mean ± SD (?) (range) duration of diabetes (years): 13 ± 10.6 (1–26) Number of patients with diabetes for less than/at least 10 years: 22/58 Number of patients without occupation/illiterate: 61/53 Proportions of patients with risk factors: body mass index of at least 25 kg/m^2: 40% Dyslipidaemia: 28% Smokers: 55% Alcohol use: 21% Peripheral neuropathy: 74.6% Vegetative neuropathy: 18.6% Arteritis of lower limbs: 46.6% Arterial hypertension: 30.6% Coronary insufficiency: 9.3% Proportion of patients with diabetes-related co-morbidity: Nephropathy: 17.3%	I1: The wound was debrided, cleaned with 3% hydrogen peroxide solution and dried with a compress. Sugar was then poured into the wound cavity, taking care to ensure that the deepest parts of the wound were filled. An occlusive dressing and bandage were applied and changed daily (n = 16) I2: As above, with the addition of systemic antibiotics. The choice of antibiotic was determined through the bacterial profile of wound samples and was modified as indicated by further cultures (n = 24) I3: The wound was debrided, cleaned with 3% hydrogen peroxide solution and dried with a compress. Systemic antibiotics were administered. An occlusive dressing and bandage were applied (n = 40)	Statistical methods: Not described Healing rate (overall): I1: 49.9% I2: 45.8% I1 and I2 combined: 47.5% I3: 40.0% ns Mean time to healing (overall): I1 & I2: 6 weeks I3: 9 weeks ns Healing rate according to site of wound: Foot: I1 and I2 combined 30.7% I3: 36.1% ns Sites other than foot: I1 and I2 combined: 100% I3: 75% $p < 0.001$ Overall healing rate for infected/neuropathic/ischaemic lesions: 66%/38.7%/37.5% $p < 0.001$ Healing rate for infected/neuropathic/ischaemic lesions treated with sugar (groups I1 and I2 combined): 66.6%/38.7%/31.5% $p < 0.001$ for infected versus neuropathic wounds and for infected versus ischaemic wounds	Not reported	Rationale for use of sugar as an antimicrobial: in their discussion, the authors cite other studies that have used sugar as a topical antimicrobial agent with wounds, and they also describe the possible physiological mechanisms involved The authors proposed that between-group differences may not have been detected for foot wounds because of the difficulty of applying sugar to the foot and because of likely concurrent neurological and vascular co-morbidities Limitations of the study as noted by the reviewer: this is a weak study in several important respects. Baseline data are not reported per group, therefore group comparability cannot be assessed. There are no baseline data on wound size or severity. Some details of interventions are lacking (e.g. the type of debridement used, and the type of sugar). Uneven numbers were

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
		Diabetic retinopathy: 53.3% Proportion of patients with wound on foot/leg/other site: 81.25%/5.00%/13.75% Proportion of patients with infected/neuropathic/ischaemic wounds: 51.7%/44.6%/33.00% In patients with foot wounds, number (%) with mal perforant plantar lesions/ischaemic lesions/lesions involving bone: 55 (68.75%)/25 (31.25%)/31 (38.75%) Proportion of patients with wounds preceded by trauma, not immediately noticed due to sensory neuropathy: 82%		Healing rate according to duration of diabetes: Less than 10 years: 54.4% At least 10 years: 36.6% $p < 0.05$ Mean ± SD (?) time to healing according to duration of diabetes: Less than 10 years: 6.4 ± 2.2 weeks At least 10 years: 10.75 ± 3.1 weeks $p < 0.05$ Healing rate according to glycaemic control: Blood sugar <2 g/l: 48.50% Blood sugar 2–2.5 g/l: 31.25 Blood sugar >2.5 g/l: 25.00% $p < 0.05$ Healing rate according to socio-economic level: Good score >6: 44.4% Moderate 3–6: 31.2% Poor <3: 23.3% $p < 0.05$ Mean ± SD (?) time to healing according to socio-economic level: Good score >6: 6 ± 1.6 weeks Moderate 3-6: 8.4 ± 2 weeks Poor <3: 10 ± 3 weeks $p < 0.05$ Cost of hospitalisation, not including treatment (overall): Average was 800 dinars (20 dinars per day) Cost of treatment (overall): Average was 194 dinars per patient (surgical procedures not included)		recruited to the study groups and this was not explained in the methods section. The study period is not clear. The mean ± SD (?) length of hospital stay was reported as 40 ± 13 days; however, an average length of stay of 15–30 days is also reported. Patients were followed up for up to 9 weeks but it is not stated whether this occurred after discharge, and if so, what treatment was provided in the interim period. The statistical methods used are not described, and it is not clear whether the reported variances are standard deviation or standard error. Healing rates are reported, but healing is not defined. There are few details about how outcomes were assessed. It is not clear in every case exactly what comparisons the reported *p*-values are referring to. Groups 1 and 2 (those involving use of sugar) are sometimes combined for analysis but this is not explained in the methods

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
				The authors estimated that by using sugar, the average cost per patient could be reduced to 21 dinars as much of the care could be carried out by the patient or his/her family at home. The methods of estimation used were not described		section. Many of the results are not reported per treatment group. In their conclusion the authors state that use of sugar does not produce adverse effects, but this was not assessed during the study. Study sponsorship: Not stated

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Seidel (1991),[110] Germany Study design: CCT Method of allocation: Patients chose their own therapy Unit of allocation: Patient Calculation of statistical power: Not stated Outcome assessment: Clinical status of ulcer: (1) purulent membranes/no improvement – score 0 points; (2) partial vascular granulation – score 1 point; (3) full vascular granulation – score 2 points; (4) diminution of ulcer – score 3 points; (5) cure – score 4 points. Planimetric measures (photographic/X-ray). Bacterial analysis (no data available). Psychological outcome (questionnaire: patient opinion of effect of treatment) Setting: Inpatients Length of treatment: 10 days	Population: male inpatients with DNPU	All male (n = 40) I1: n = 20 I2: n =20 Age: 45–70 years Mean age of initial DNPU manifestation: 62 (± 5 years) Type of diabetes: Type I: 8/40 (20%) Type IIa: 14/40 (35%) Type IIb: 18/40 (45%) Bacteriology: No data Clinical status of ulcer (score): I1 I2 Purulent membranes 9 10 Partial vascular granulation 9 8 Full vascular granulation 2 2 Patients with osteomyelitis: I1: 5/20 (25%) I2: 7/20 (35%)	I1: (n = 20) Patients received a perfusion (once daily) of RVP (comprising 120 mg gentamicin, 50 mg buflomedil, 4 mg dexamethasone, 4 mg lignocaine and 2500 IU of heparin dissolved in 120 ml saline solution). After aseptic puncture of a foot vein, the leg is drained by high elevation for 2 minutes and then mid/upper leg compressed at 30 mm/Hg above the systolic arterial pressure. The 'cocktail' is then injected as a bolus. Additional evening medication of 60 mg gentamicin i.m. and one retard tablet of buflomedil. For reasons of comparability an additional infusion therapy with 3 × 4 g piperacilline also given I2: (n = 20) Treated conventionally with 3 × 4 g piperacillin, 3 × 60 mg gentamicin, 3 x 50 mg buflomedil, 3 × 500 ml dextran 40 and 3 × 5000 IU heparin daily Both groups received same regimen of local antibacterial therapy	Ulcer healed: I1: 6/20 (30%) I2: 0/20 (0%) Ulcer diminished in size: I1: 10/20 (50%) I2: 3/20 (15%) % Diminution of ulcerous pain (not clear whether this is pain or area?): I1: 55% ± 8 I2: 7.5% ± 3.6 Debridement of exudative detritus: I1: 93% ± 3 I2: 42% ± 8 Reduction in infectious ulcer cover: I1: 86% ±3.7 I2: 38% ± 8 Hospitalisation (average days): I1: 12 ± 2 I2: 19 ± 3 Amputation: I1: 0/20 (0%) I2: 4/20 (20%) (due to underlying osteomyelitis) Cure of osteomyelitis (%): I1: 4/5 (80%) I2: 0/7 (0%) HbA1c (%): I1: 8.1 ± 1.0 I2: 8.9 ± 1.0 Questionnaire results: Distinct difference between groups with I1 group showing	Not stated	Limitations of the study: Patients chose their own therapy 10% more cases of osteomyelitis in I2 group at baseline? No demographic comparability of groups reported, e.g. age data/type of diabetes, area of ulceration Authors say the improvement in patient knowledge was because the 30-minute treatment time allowed patient to ask doctor questions, patient training could be delivered

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
				greater perception of physical/emotional improvement. Compliance and individual knowledge about the disease also higher in this group Bacterial profile: no results given Adverse events (RVP): Petechiae: 6/20 (30%) Pain (from arterial occlusion): 5/20 (25%) Haemorrhage: 4/20 (20%) Stasis dermatitis: 3/20 (15%) Nausea: 2/20 (8%) Reversible NVIII affection: 1 (5%) (temporary decrease in hearing capacity)		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Seidel (1993, 1994),[111,112] Germany (German translation of paper) Study design: CCT Method of randomisation: Patients chose their own therapy Unit of allocation: Patient Calculation of statistical power: Not stated Outcome assessment: (as Seidel *et al.*, 1991[110]) Setting and length of treatment (inpatients as Seidel *et al.*, 1991[110]). Treatment over 10 days. Date of recruitment: December 1989	Population: male inpatients with DNPU	Males: 45 Age: 35–70 years Mean ± SD age (years): 60 ± 4 Type of diabetes: Type I: 8 (17%) Type IIa: 14 (35%) Type IIb: 23 (48%) Clinical status of ulcer: I1: Pus 10, Partial 11, Full 3 I2: Pus 9, Partial 9, Full 3	I1: (n = 24) RVP netilmycin Patients given (10 a.m.) 200 mg netilmycin; 50 mg bufedil; 200 IU heparin; 4 mg dexamethasone; 2 mg lidocaine (all in 100 ml 0.9% saline). At 6 p.m.: 100 mg netilmycin (i.m.); 600 mg bufedil retard (oral); 4 g piperacillin twice a day (i.v.) I2: (n = 21) SVI – netilmycin Patients given (at 9 a.m., 3 p.m., 9 p.m.) 100 mg netilmycin; 50 mg bufedil; 2500 I.U. heparin all in rheomacrodex. At 9 a.m. – 4 mg Dexamethasone. 4 g piperacillin twice a day (i.v.). Concurrent treatment i.v.: Cleansed with hydrogen peroxide, povidone iodine pad, sterile bandage. Dietary and medical treatments for diabetes	I1 / I2 Ulcer healed: 8 (33%) / 3 (14%) At least 30% reduction in area: 10 (42%) / 4 (19%) Reduction in purulent area: 93 ± 6 / 42 ± 8 Amputation: 3 (13%) / 4 (19%)		

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Tan (1993),[108] USA Study design: RCT (double-blind) Method of randomisation: Computer-generated schedule. 3:2 ratio I1:I2 to allow larger safety database for registration of I1 drug Unit of allocation: Patient Calculation of statistical power: Estimated approximately 50% of randomised patients (sample size I1 $n = 150$ and I2 $n = 100$) would be evaluable for primary analyses. Projected evaluable patients provided a power of 70% for observed treatment difference (significance: $\alpha = 0.05$, two-tailed) if the true treatment difference in underlying population not more than 20%. All patients qualified for intention to treat analysis. Projected numbers provided power of 82% for observed treatment difference (significance, $\alpha = 0.05$, two tailed) if true treatment difference was no more than 15%	Population: 251 hospitalised patients with complicated skin/skin structure infections (age 16+ years) Inclusion criteria: Purulent drainage or collection plus at least 3 of the following: temperature >38°C, peripheral leukocyte count >10,000/mm^3 (with >5% immature neutrophils), local erythema, local swelling, tenderness, pain, or fluctuance. Severity assessed by investigator as mild, moderate or severe at baseline Exclusion criteria: Known or suspected hypersensitivity to beta-lactam antibiotics or β-lactamase inhibitors; moderate to severe renal dysfunction; evidence of active liver disease; peripheral granulocyte counts	Total no. of participants: I1: (all) 153, (evaluable) 67 I2: (all) 98, (evaluable) 44 Male/female (numbers): I1: (all) 115/38, (evaluable) 53/14 I2: (all) 69/29, (evaluable) 32/12 Ethnicity (numbers): All / Evaluable I1: Caucasian 111 / 43 Black 29 / 12 Other race 13 / 12 I2: Caucasian 69 / 29 Black 20 / 8 Other race 9 / 7 Age: mean ± SD (years): I1: (all) 53, (evaluable) 53 I2: (all) 52, (evaluable) 55 Number/% with diabetic foot ulcers (classed as 'wound infection' by author): I1: (all) 31 (20), (evaluable) 16 (24) I2: (all) 18 (18), (evaluable) 7 (16) Prior/current use of antimicrobial agents: see Exclusion criteria	I1: ($n = 153$) Patients dosed every 6 hours with piperacillin–tazobactam, 3 g and 375 mg, respectively for a minimum of 5 days and for at least 48 hours after the resolution of signs and symptoms. I2: ($n = 98$) Patients dosed every 6 hours with ticarcillin–clavulanate, 3 g and 100 mg, respectively, for a minimum of 5 full days and for at least 48 hours after the resolution of signs and symptoms Surgical debridement or drainage allowed and accepted as part of patient management. Need for surgery or other adjunctive therapy was determined by the investigator and the collaborating surgeon	Statistical methods: numbers (%); Wilcoxon, χ^2 tests. [significance testing – α (two-tailed) = 0.05] Mean duration of treatment (days) I1: (all) 8.2, (evaluable) 10.2 I2: (all) 9.1, (evaluable) 10.5 Evaluable patients divided by diagnosis: 1st: Cellulitis 2nd: Cutaneous abscess 3rd: Diabetic or ischaemic foot infection 4th: infected wounds and ulcers – includes pressure ulcers on the foot. Clinical response (no. group and % group) for wound or ulcer infection [these were evaluable patients with diabetic foot ulcers, as confirmed by author]: I1: Cured 9/16 (56) Improved 1/16 (6) Favourable 10/16 (63) I2: Cured 6/7 (86) Improved 1/7 (14) Favourable 7/7 (100) ($p = 0.17$) Clinical failures (wound/ulcer patients): I1: 2 (switched to another antibiotic)	Clinical failures: I1: 5 I2: 4 3 patients in each treatment arm due to amputation of infected limb. 2 patients in I1 and 1 in I2 switched to another antibiotic	Query whether those with wound infection (authors say these were foot ulcer patients) were also diabetic? Sharp reduction in numbers available for final evaluation Evaluability criteria: Failure to meet criteria for diagnosis; no baseline pathogen, inadequate clinical follow-up; pre-study antibiotic; concomitant infection; resistant pathogen at baseline; other (incorrect diagnosis, inadequate drug susceptibility data, inadequate bacteriological follow-up, inadequate treatment regimen) Study sponsorship: Infections Limited? Multi-centre (20 sites)

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Outcome assessment: Clinical: (1) Cured: recovery from infection; (2) improved – showed improvement in at least 3 of the following parameters compared with values obtained at pre-enrolment evaluation: quantity of drainage, erythema, severity of swelling, tenderness, pain, fluctuance, lymphangitis, rigors, temperature, peripheral leucocyte count; (and no new antimicrobial therapy necessary) (1) and (2) Classed as favourable clinical response. (3) Unfavourable: relapse from initial improvement and worsening of parameters above, or failure, requiring change in antimicrobial therapy. They used 2 sets of outcome criteria – registration criteria (used for drug registration purposes) and revised outcome determinations Clinical failures: criteria (1) amputation at infection site, even if	of $<1000/mm^3$ or platelet counts of $<50,000/mm^3$; receipt of more than 2 doses of another antibacterial agent within 72 hours prior to enrolment; receipt of another investigational drug within 1 month prior to enrolment; active or treated leukaemia; AIDS; need for haemodialysis, peritoneal dialysis, plasmapheresis or hemoperfusion, osteomyelitis contiguous with a skin/skin structure infection; potential requirement for amputation of infected area; pressure ulcer infections of >2 weeks duration; concomitant infection other than skin/skin structure infection			Endpoint eradication of bacterial pathogens (isolated from the infected site in evaluable patients): Total no. of isolates eradicated/no. of isolates recovered (%) I1 I2 Total 103/135 (76) 82/99 (82.8) Adverse events (all patients experiencing at least one adverse event): I1: 65 (42%) I2: 41 (42%) Of which: I1: 11% gastrointestinal tract 6.5% diarrhoea I2: 11% gastrointestinal tract 4.1% diarrhoea (ns) between groups		

continued

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
non-infection-related of improvements observed, or (2) patient switched to oral antibiotics even if they had little or no infection at that time, established to assess efficacies of drugs for registration purposes Bacteriological outcomes: Organisms isolated from evaluable patients and frequency with which they were eradicated. Eradication: baseline pathogens eradicated. Eradication presumed: improvement but no material available for analysis. Persistence: at least one pathogen from initial sample still present at follow up. Persistence presumed: unfavourable response but no material available for analysis Setting and length of treatment: Multi-centre (20) hospital setting. Minimum 5 day treatment plus at least 48 hours after resolution of signs and symptoms. Early follow-up: 24–72 hours after therapy completion. Late follow-up: 10–14 days after therapy completion						

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Vandeputte (1996)[125] Belgium Study design: RCT Method of randomisation: Pre-prepared randomised listing Unit of allocation: Patient Calculation of statistical power: Not stated Outcome assessment: Wound healing time (by photographic measure every 4 weeks); pressure relief, mobility, dressing durability, infection during trial, callus formation, need for systemic local antibiotics or antiseptic creams, amputation. Patient interviewed during trial about comfort and pain Setting: Not stated Length of treatment: 3 months Written consent	Inclusion criteria: 29 diabetic patients with foot ulcers (neuropathic or not) Exclusion criteria: Patients taking systemic antibiotics	Numbers in study: I1: 15 I2: 14 Male/female: I1: 7/8 I2: 6/8 Mean ± SD age (years): I1: 62.6 (14.7) I2: 65.3 (14.3) Completely mobile: I1: 12/15 (80%) I2: 11/14 (79%) Treated with oral antidiabetic medication/insulin dependent: All patients received optimal insulin treatment and diet regulation (according to international recognised diabetic regulation protocols) Evidence of neuropathy: I1: 9/15 (60%) I2: 9/14 (64%) Infection present before trial: I1: 1/15 (7%) I2: 1/14 (7%)	I1: Patients (n = 15) treated with hydrogel dressing and dermal wound cleanser (Flami-Clens = saline water + 0.8% vinegar acid as buffer). (From previous data extraction: wound cavities were filled with an alginate dressing) I2: Patients (n = 14) treated with a dry gauze (twice a day) and irrigated with chlorhexidine (0.05% solution). [From previous data extraction: all patients received systemic or topical antibiotics or topical antiseptic creams. 6 patients received systemic antibiotics. The most frequently used topical preparation was povidone-iodine cream]	Mortality: I2: 2 patients died during trial Amputation (one or more toes): I1: 1/15 (7%) I2: 5/14 (36%) ($p < 0.053$) Patient could walk with dressing on: I1: 12/15 (80%) I2: 9/14 (64%) ($p < 0.01$) Average time dressing stayed on wound: I1 5 days I2: 1 day ($p < 0.001$) Infection during trial: I1: 1/15 (7%) I2: 7/14 (50%) ($p < 0.01$) Formation of callus: I1 7/15 (47%) I2: 14/14 (100%) ($p < 0.05$) Need for systemic/local antibiotics or local antiseptic creams: I1: 1/15 (7%) I2: 14/14 (100%) ($p < 0.0001$) Complete healing at 3 months: I1: 14/15 (93%) I2: 5/14 (36%) ($p < 0.05$) Improved slightly: I1: 0/15 (0%) I2: 1/14 (7%) ($p < 0.05$) Not improved: I1: 1/15 (7%) I2: 4/14 (29%) ($p < 0.05$)	2 patients died (I2 group) during trial	Relevance to DASIDU are findings for control group (chlorhexidine). Compared with use of hydrogel, control group required additional local antibiotics/antiseptics, had higher incidence of amputations, and greater healing time required. Possibly/probably not intention-to-treat analysis as they excluded the patient who died from the analysis

Study and design	Participants	Baseline characteristics	Intervention details	Results	Withdrawals	Comments
Yonem (2001),[120] Turkey Study design: RCT Method of randomisation: Not specified Unit of allocation: patient Calculation of statistical power: Not specified Outcome assessment: Primary: time to resolution of infection, time to hospital discharge Secondary: need for surgical intervention, effects of G-CSF on neutrophil function Setting and length of treatment: Not specified/not clear	Inclusion criteria: 30 diabetic patients with pedal cellulitis or Wagner's classification grade 2 or less foot lesion Exclusion criteria: Presence of haematological disease, history or previous or current malignancy, renal or hepatic failure, pregnant or lactating, severe leg ischaemia, deep or severe infections, receiving immunosuppressive therapy. Absolute neutrophil count $<1.5 \times 10$ (9)/l or $>20 \times 10$ (9)/l	Male/female: I1: 9/6 I2: 8/7 Mean ± SD age (years): I1: 61 ± 1.4 I2: 60.3 ± 1.3 Mean ± SD duration of diabetes (years): I1: 12.7 ± 0.9 I2: 13.5 ± 1.2 Neutrophil count/mm^3: I1: 5700 ± 600 I2: 5200 ± 500 Phagocytosis test (%): I1: 68.1 ± 2.2 I2: 70.4 ± 2.0 Respiratory burst (mV): I1: 2.0 ± 0.4 I2: 1.6 ± 0.3 No significant differences reported between groups on above criteria	Cultures for aerobes and anaerobes taken from the ulcers with an appropriate technique. Then: I1: 15 patients in the 'standard group' received classical treatment comprising a combination of local wound care and antibiotherapy (intravenous ciprofloxacin and metronidazole) I2: 15 patients in the 'G-CSF group' received the above classical treatment, plus recombinant human G-CSF [Filgrastim (Neupogen)]. G-CSF (5 μg/kg) administered subcutaneously once daily. If the absolute neutrophil count was $>30 \times 10$ (9)/l after 3 consecutive doses, the dose was changed to 2.5 μg/kg daily on alternate days. If total white blood cell count was $>70 \times 10$ (9)/l or the absolute neutrophil count was $>45 \times 10$ (9)/l, G-CSF treatment was stopped All patients placed on daily multiple-dose injection of short-acting insulin	Statistical methods: Mann–Whitney *U*-test, Wilcoxon matched pairs, signed ranks and χ^2 tests. Spearman correlation analyses. Means ± SD. Significance between study groups Time to resolution of infection (days): I1: 22.3 ± 1.7 I2: 23.6 ± 1.8 ns Duration of hospitalisation (days) I1: 28.3 ± 2.2 I2: 26.9 ± 2.0 ns Need for surgical intervention (amputation): I1: 3 (20%) I2: 2 (13.3%) ns Effect on neutrophils (post-treatment): Neutrophil count (mean ± SD): I1: 4800 ± 300/mm^3 I2: 48700 ± 1000/mm^3 $p < 0.001$ Phagocytosis test (%): I1: 69.4 ± 1.9 I2: 74.5 ± 1.9 ns Respiratory burst (mV): I1: 2.3 ± 0.4 I2: 2.3 ± 0.5 ns Duration of parenteral A/B: I1: 23.3 ± 1.9 I2: 22.9 ± 2.0 Adverse events: none	Not stated	Authors draw attention to very limited effectiveness of G-CSF in the treatment of diabetic foot infection. However, study lacks power Written informed consent. Local ethics approval obtained High white blood cell counts may predispose to coronary/ cerebrovascular events

Cost-effectiveness data extraction tables

Study identifier and objective	Key elements of the study	Clinical effectiveness data	Economic analysis	Results	Comments
Apelqvist (1996),[122,126] Sweden Study objective: To compare the clinical effect and economic cost of cadexomer iodine with that of standard treatment in diabetic patients with cavity foot ulcers	Type of economic evaluation: CEA Since no differences in clinical results were observed, a cost-minimisation analysis was performed Perspective: Health service Setting: Lund, Sweden Dates to which data relate: The dates to which the effectiveness analysis and resource use data referred were not reported. Price year was 1993 Currency: Swedish Kroner (SEK). A conversion to UK pounds was performed using a 1993 exchange rate of £1= SEK12.10. A conversion to US dollars was performed using a 1993 exchange rate of US$1= SEK8.10	Source: Single RCT Details of participants, interventions, outcomes and results of the clinical trial are summarised above (clinical effectiveness table) Link between clinical effectiveness and cost data: The data for the economic evaluation were collected during the clinical trial	35 patients were included in the economic analysis Measure of health benefits used: No summary benefit measure was used, and only separate clinical outcomes were reported Resource use: Frequency of dressing changes, drug prescription, material consumption and time involved were recorded. Type of dressings/drugs, person who changed dressings, time involved, and location of dressing change were documented Description of costs: Direct costs were estimated for dressing materials, drugs, staff and transport. The authors stated that, since most patients in the study were above working age, no indirect costs for lost production were estimated. Costs and quantities were reported separately. The operating costs (materials and drugs, staff and transport) and cost of complications were measured. The estimation of quantities and unit costs was based on actual data apart from those for transport. The average values for transport for the patient to visit an outpatient care unit or for the staff to visit the patient at home were estimated in terms of distance/price at 10 km/SEK24.50. If the patient or a relative living in the same household performed the dressing change, no	Estimated health benefits used in the economic analysis: Not applicable Resource use: Mean (range) dressing changes per week, and adherence: C: 9.9 (3.1–13.9) Lower mean than expected – prescribed once or twice daily: I: 4.7 (3.2–6.9) Higher mean than expected – prescribed daily during week 1 and daily or every 2 or 3 days thereafter Number (%) dressing changes performed by: Nurse C: 591 (30.0%) I: 210 (26.8%) Auxiliary nurse C: 1,095 (55.6%) I: 350 (44.6%) Patient or spouse C: 7 (0.4%) I: 113 (14.4%) Other C: 276 (14.0%) I: 112 (14.3%) Mean (range) minutes per dressing change: C: 11 (5–23) I: 13 (8–24) Type of dressing (number of patients treated C/I): Cadexomer iodine 0/17 Gentamicin solution 14/0	Notes about duplicate publication: See clinical effectiveness table (pp. 134–5) Limitations of the study, as noted by the study authors: 1. Patients should be followed up until final outcome (complete healing or death). However, it may be difficult to collect accurate data on resource use if data are collected over a longer period of time 2. No time costs were calculated for patients or relatives who changed dressings without help from the healthcare system 3. Patients in a clinical trial may be more closely monitored and treatment patterns may differ from normal clinical practice. More resources may therefore be consumed Adherence with therapy may be lower in regular practice than in a trial. In the future, it may be advisable to make adjustments to the economic evaluation in order to reflect clinical practice

continued

Study identifier and objective	Key elements of the study	Clinical effectiveness data	Economic analysis	Results	Comments
			travelling costs and no labour costs were estimated. The source of quantities was the study records. The dates during which the quantities were measured were not reported Information on prices for drugs and materials was obtained from FASS (1995): Läkemedel i Sverige. Stockholm, Sweden (Läkemedelsinformation AB, 1995) and current market prices. The average wages for nursing staff in 1991, with non-wage labour costs added (taxes, national insurance), were adjusted to 1993 prices. Labour costs included the time required to prepare for the dressing change, to redress the wound and to tidy up after the procedure. If travelling was involved, an extra 30 minutes was added to the treatment time. The costs of outpatient visits, which were thought not to differ in frequency between treatment options, were excluded Methods used for statistical analysis of quantities and costs: The Mann–Whitney *U*-test (two-tailed) was used the compare costs between the two groups Assumptions used: 1. Weekly resource costs will remain constant until complete healing. 2. The healing rate in patients in group I will be at least as good as in patients in group C until complete healing occurs	Streptodornase/streptokinase 2/0 Dry saline gauze 9/1 Vaseline gauze 6/8 Mean (range) weeks of treatment: C: 11 (5–12) I: 10 (1–12) Cost results: Mean (range) weekly staff (SEK): C: 884 (315–1492) I: 380 (96–570) $p < 0.001$ Mean (range) weekly transport costs (SEK): C: 243 (76–341) I: 100 (29–156) $p < 0.001$ Mean (range) weekly cost for materials and drugs SEK: C: 294 (37–981) I: 423 (166–1113) ns Mean (range) total weekly (SEK): C: 1421 (428–2679) I: 903 (524–1697) $p < 0.01$ Synthesis of costs and benefits Weekly cost per patient healed: C: SEK12,790 I: SEK3070 ns Sensitivity analyses: 1. The results were sensitive to the assumptions about travelling distance and time. If a travelling distance of 5 instead of 10 km was assumed, the	Study sponsorship: Perstorp Pharma, Lund, Sweden, and the Swedish Diabetes Association

continued

Study identifier and objective	Key elements of the study	Clinical effectiveness data	Economic analysis	Results	Comments
			Methods used for sensitivity analyses: The parameters used were transport costs, type of staff performing the dressing, the ability of patients to change their ulcer dressings without help from the health care staff and strict adherence with physicians' prescriptions. Also, one (originally excluded) hospitalisation was included in the analysis and the corresponding results were compared Synthesis of costs and benefits: Although a synthesis of costs and benefits was not required due to the intervention being a dominant strategy, the weekly cost per patient healed was calculated	estimated time for travelling was assumed to be reduced by 15 minutes, resulting in a reduction of the total weekly cost of 20% for patients treated with cadexomer iodine and 31% for patients treated with the control regimen. Travelling costs would be 50% lower in both groups, whereas staff costs would be 35 and 36% lower, respectively. 2. If patients or relatives living in the same household could perform 50% of the dressing changes, total weekly costs would decrease by 27% in I and by 40% in C. 3. Staff category: the reduction in total weekly costs if all dressing changes were performed by auxiliary nurses compared with if nurses perform all the changes is 7% for I patients and 9% for C patients. 4. Adherence: if patients were treated exactly according to prescription, the total weekly cost would be SEK836 for patients treated with cadexomer iodine and SEK1914 for patients treated with the control regimen (assuming that staff proportion and average treatment time were the same as in this study). 5. Results were also sensitive to a possible adverse reaction resulting in hospitalisation. Based on data from one patient who was hospitalised due to fever, the total costs were estimated as SEK9916 for group I and SEK8910 for group C, and weekly costs were estimated as SEK 1040 for group I and SEK903 for group C	

CEA, cost-effectiveness analysis.

Study identifier and objective	Key elements of the study	Clinical effectiveness data	Economic analysis	Results	Comments
McKinnon (1997),[113] USA To compare the cost-effectiveness of A/S (I1 group) versus I/C (I2 group) in the treatment of diabetic foot infections. See Grayson *et al*. (1994)[44] for effectiveness data extraction Person investigating was unaware which regimen was used for each patient	Type of economic evaluation: CEA Perspective: Institution (hospital) Settings of clinical effectiveness study and economic evaluation: Deaconess Hospital Podiatry Services, Boston, MA, USA Clinical trial was over 1 year; 1994 prices (US $) used. No specific dates, but economic evaluation started on day study-drug treatment initiated and ceased when antibiotic administration stopped (unless treatment not successful, in which case subsequent costs were calculated)	Source: Single study (double-blind, RCT). Details of participants, interventions and results of clinical effectiveness given in Grayson *et al*. (1994).[44] Economic data available for 90/93 of the original sample. (I1, $n = 45$, I2, $n = 45$) Economically significant adverse events (i.e. requiring treatment and relating to study drug or of unknown origin) I1: 7 (16%) I2: 9 (20%) Due to: Diarrhoea: I1: 1 I2: 4 Seizure: I1: 0 I2: 1 Other[a]: I1: 6 I2: 4 [a] Rash, nausea/vomiting or fungal superinfection	Measure of health benefits used: No clinically significant differences were found between the two treatment regimens, therefore economic analysis compared costs only Costing undertaken retrospectively Description of costs: Three levels of analysis: Level I: acquisition price of medication (based on nationally published direct drug prices in 1994) Level II: level I costs, plus all costs directly related to antibiotic use and infection treatment, excluding cost of a hospital bed. Antibiotic-related items include acquisition cost, medication preparation (average $4 per intravenous dose) and administration, treatment of adverse events, secondary treatment of failures Level III: all level II costs plus hospital bed costs. Average value for hospital bed use in US ($852/day) was applied ALOS (antibiotic-related length of stay) used to calculate the costs of hospital stay directly related to the treatment. Raw LOS (length of stay) data were also calculated No discounting necessary as costs and outcomes occurred during same time period Currency: US$	Estimated health benefits used in the economic analysis: not applicable Cost results: Mean level I costs per patient ($): I1: $603 (SD 313) I2: $1307 (SD 816) ($p < 0.001$) Mean level II costs per patient ($): I1: $982 (SD 650) I2: $1654 (SD 913) ($p < 0.001$) Mean level III costs per patient ($): I1: 14,084 (SD 8262) I2: 17,008 (SD 9064) ($p = 0.05$) Mean total treatment cost was $3000 less per patient in I1 than in I2. Given that no significant differences were found between treatments in effectiveness study, cost-effectiveness was maintained for I1 Sensitivity analysis results: I2 (I/C) would need to be 30% more effective than I1 (A/S) in order to become cost-effective as defined in the parameters of this study	Limitations of the study (as noted by the authors): Retrospective analysis cannot satisfy criteria for comprehensive evaluation as not all desired data were collected (e.g., potential differences in LOS in intensive care units) at the time of the trial Results limited to moderate severity infections. Authors advise cautious approach in generalising to severe/life-threatening infections Data not collected on laboratory tests, surgery, physical therapy, radiotherapy, etc. Not generalisable to more severe infections University of York, Centre for Reviews and Dissemination (CRD) commentary: 1. Selection of comparators: clear 2. Validity of estimate of measure of benefits: likely to be internally valid, although some details with regard to the adequacy of study size are missing 3. Validity of estimate of costs: methods of cost estimation clearly

continued

Study identifier and objective	Key elements of the study	Clinical effectiveness data	Economic analysis	Results	Comments
			Methods used for statistical analysis of quantities and costs: Means, SD and Kruskal–Wallis one-way ANOVA used to compare LOS, ALOS and costs associated with the two regimens Method used for sensitivity analyses: Decision tree Drug acquisition price tested 25% above and below direct price for each antibiotic ($9–15 for 3 g of A/S and $17–30 for 500 mg of I/C) Hospital bed cost $852 ± $250, varied for a range of $600–1100 Probability of treatment success varied independently between 50% and 95% to encompass possible outcomes		explained. Authors felt that direct measurement of resources and prices would have been preferable, but they have produced a general cost estimate. Although some costs were omitted (e.g. differences in length of intensive care unit stay), all the most important cost elements were included in the analysis Study sponsorship: Partly supported by Pfizer Pharmaceuticals

ANOVA, analysis of variance; C, control group; CEA, cost-effectiveness analysis; I, intervention group; I1, first intervention group; I2, second intervention group.

Appendix 5

Quality assessment

Quality assessment of diagnostic studies

Item		Study		
		Gardner et *al.* (2001)[90]	**Bill et *al.* (2001)[91]**	**Ratliff and Rodeheaver (2002)[92]**
1.	Was the spectrum of patients representative of the patients who will receive the test in practice?	No	Yes	Yes
2.	Were selection criteria clearly described?	Yes	Yes	Yes
3.	Is the reference standard likely to classify the target condition correctly?	Unclear	Unclear	Unclear
4.	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Yes for 3 out of 4 study centres that participated in the evaluation	Yes	Unclear
5.	Did the whole sample or a random selection of the sample receive verification using a reference standard of diagnosis?	Yes	Yes	Yes
6.	Did patients receive the same reference standard regardless of the index test result?	Yes	Yes	Yes
7.	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?	Yes	Yes	Yes
8a.	Was the execution of the index test described in sufficient detail to permit replication of the test?	Yes	Yes	Yes
8b.	Was the execution of the reference standard described in sufficient detail to permit its replication?	Yes	Yes	Yes
9a.	Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear	Unclear	Unclear
9b.	Were the reference standard results interpreted without knowledge of the results of the index test?	Unclear	Unclear	Unclear
10.	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Unclear	Unclear	Unclear
11.	Were uninterpretable/intermediate test results reported?	No[a]	No[a]	No[a]
12.	Were withdrawals from the study explained?	No[a]	No[a]	No[a]

[a] No, not applicable as there did not appear to be any uninterpretable results or withdrawals.

Quality assessment for RCTs and CCTs

Study	Score for randomisation[a]	Score for double blinding[b]	Score for reporting of withdrawals[c]	Score for allocation concealment[d]
Apelqvist (1996)[122]	2	0	0	C
Bouter (1996)[106]	2	0	1	C
Bradsher (1984)[43]	2	0	1	B
Chantelau (1996)[74]	2	1	0	B
de Lalla (2001)[119]	1	0	1	B
Dwivedi (2000)[127]	1	0	0	B
Erstad (1997)[107]	1	1	1	B
Gough (1997)[100]	2	2	1	A
Grayson (1994)[44]	2	1	1	B
Kastenbauer (2003)[118]	1	0	1	B
Lipsky A[114]	1	2	1	B
Lipsky B[114]	1	2	1	B
Lipsky (2004)[109]	1	0	0	B
Lipsky (1990)[75]	1	0	1	B
Marchina (1997)[123]	1	0	NA	B
Markevich (2000)[105]	1	0	0	B
Peterson (1989)[101]	2	1	1	A
Rhaiem (1998) [124]	1	0	0	B
Seidel (1991)[110] (CCT)[e]				
	NA	Patients chose therapy. Baseline comparability: unclear. Adjustments: none	0	C
Seidel (1993,1994)[111, 112] (CCT)[e]	NA	Patients chose therapy. Baseline comparability: unclear. Adjustments: none	0	C
Tan (1993)[108]	2	1	1	B
Vandeputte (1996)[125]	2	0	1	B
Yonem (2001)[120]	1	0	0	B

NA, not applicable

[a] *Randomisation. score: 0 or 1 or 2*. One point was given if the study described using words such as random or randomisation. One extra point was given if the method of randomisation was described and was appropriate. One point was deducted if the method of randomisation was described and was considered to be inappropriate.

[b] *Double-blinding. score: 0 or 1 or 2*. One point was given if the study was described as double-blind. One extra point was given if the method of double-blinding was described and was appropriate. One point was taken away if the method of double-blinding was described and was inappropriate.

[c] *Withdrawals. score: 0 or 1*. One point was given if the number and reasons for withdrawals in each group were stated.

[d] *Allocation concealment. score: A or B or C*. A, Adequate: if adequate measures were taken to conceal allocation. B, Unclear: if report of allocation concealment was not reported or did not fit in category A or C. C, Inadequate: trials in which allocation concealment was inadequate.

[e] The critical appraisal of CCTs included the points above, with the exception of the first (randomisation). In CCTs the following additional items were assessed: method of allocation to treatment groups; degree of baseline comparability between treatment groups; and appropriateness of adjustment during data analysis for observed imbalances between treatment groups.

Quality assessment of economic evaluations

Criterion	Study	
	Apelqvist *et al.* (1996)[122]	**McKinnon *et al.* (1997)[113]**
1. Was a well-defined question posed in answerable form?		
• Study examined both costs and effects?	Y	Y
• Study involved a comparison of alternatives?	Y	Y
• Viewpoint for analysis stated?	Y	Y
2. Was a comprehensive description of the competing alternatives given?		
• Any important alternative omitted?	N	Unclear
• Was a 'do nothing' alternative considered?	N	NA
3. Was the effectiveness of the programmes or services established?		
• Was it via an RCT? If so did the protocol reflect real practice?	Y	Y
• Was it via an overview of clinical studies?	N	N
• Were observational data or assumptions used to establish effectiveness. If so what are the potential biases?	N	N
4. Were all the important and relevant costs and consequences for each alternative identified?		
• Was the range wide enough for the research question?	Y	Y
• Did it cover all relevant viewpoints?	Y	Y
• Were capital and operating costs included?	N	N
5. Were costs and consequences measured accurately in appropriate physical units?		
• Were any items omitted from the measurement? If so, does this mean they carried no weight in the subsequent analysis?	N	N
• Were there any circumstances that made measurement difficult? If so, were these handled appropriately?	N	N
6. Were costs and consequences valued credibly?		
• Were the sources of values clearly identified?	Y	Y
• Were market values employed for changes involving resources gained or depleted?	Y	Y
• Where market values were absent, or market values did not reflect actual values, were adjustments made?	Y	NA
• Was the valuation of consequences appropriate for the question?	Y	Y
7. Were costs and consequences adjusted for differential timing?		
• Were costs and consequences that occur in the future discounted?	N	NA
• Was any justification of the discount rate used given?	N	
8. Was an incremental analysis of costs and consequences of alternatives performed?		
• Were the incremental costs generated by one alternative over another compared with the additional benefits?	Y	NA
9. Was allowance made for uncertainty in the estimates of costs and consequences?		
• If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	Y	Y
• If a sensitivity analysis was employed, was justification provided for the range of values?	N	N
• Were study results sensitive to changes in values?	Y	Y
10. Did the presentation and discussion of study results include all issues of concern to users?		
• Were the conclusions of the analysis based on an overall index or ratio of costs to consequences? If so, was the index interpreted intelligently?	N	NA
• Were the results compared with those of others who have studied the same question?	N	N
• Did the study discuss the generalisability of the results?	N	Y
• Did the study take account of other important factors in the choice or decision, e.g. ethics?	Y	N
• Did the study discuss issues of implementation, such as feasibility of the preferred programme?	N	N

Appendix 6

Summary of excluded studies

Summary of excluded diagnostic studies[a]

Study	Description	Reason for exclusion
Basak (1992)[177]	Evaluation of microbiology of burns, traumatic wounds and pressures sores using wound swab and tissue biopsy	No DFUs or venous leg ulcers in the sample
Bessman (1992)[178]	Comparison of prevalence of diphtheroids in reliable (derived from deep tissue intra-operatively) and non-reliable cultures (specimen taken at bedside) in patients with diabetic foot infection	Unclear how many patients had ulceration; 2 × 2 diagnostic data not reported
Buntinx (1996)[179]	Assessment of several different types of wound classification systems, including one for assessing clinical signs of infection, in wounds of various aetiologies including venous leg ulcers	Assessment of inter-observer variation, not diagnostic performance
Cooper (1995)[180]	Assessment of the association between clinical signs of infection and the presence of Lancefield group G streptococci detected by wound swab in venous leg ulcers	Swabs were processed exclusively for the detection of streptococci, and the presence of other pathogens could not be excluded. There was therefore no diagnostic verification for the presence of wound infection
Crerand (1996)[181]	Description of various investigations done in a series of patients with clinically infected DFUs	Focus of study was diagnosis of osteomyelitis rather than wound infection; no diagnostic verification
Cutting (1994)[93]	Description of criteria for identifying wound infection	Description of clinical signs and symptoms, not an evaluation
Davies (2001)[38]	Description of molecular techniques in analysing the microflora of chronic wounds	Description of molecular techniques, not an evaluation
Edwards (2000)[182]	Comparison of different methods of swabbing in acute or chronic wounds	Unable to ascertain whether the sample included people with DFUs or venous leg ulcers; no outcome data available
Greenwood (1997)[183]	Pilot study of electronic aroma detection to determine changes in aroma of venous leg ulcers	No diagnostic verification
Huovinen (1992)[184]	Letter to the editor reporting an evaluation of fine needle aspiration biopsy, curettage and swab used to detect infection in leg ulcers	2 × 2 diagnostic data not available
Johnson (1995)[37]	Use of needle aspiration and swab to detect anaerobic bacteria in DFUs	2 × 2 diagnostic data not available
Kessler (2002)[185]	Evaluation of adverse effects and microbiological identification of thin needle puncture compared with superficial swab for DFUs	2 × 2 diagnostic data not available
Lee (1985)[186]	Evaluation of fine-needle aspiration biopsy and wound swab in patients with wounds of various aetiologies, including DFUs and venous leg ulcers	2 × 2 diagnostic data not available
Levine (1976)[187]	Evaluation of swab and smear versus flamed tissue biopsy in patients with burns	Sample did not include people with DFU or venous leg ulcers; 2 × 2 diagnostic data not reported

continued

Study	Description	Reason for exclusion
Lorentzen (1999)[188]	Evaluation of the Red–Yellow–Black wound classification system used with various types of chronic wounds	Assessment of inter-observer variation, not diagnostic performance
Neil (1997)[189]	Comparison of swab culture and tissue culture used to detect bacterial counts and identification in chronic wounds	Wound aetiologies unclear; no diagnostic verification of wound infection
Pellizzer (2001)[33]	Comparison of wound swab and deep tissue biopsy in DFUs	No diagnostic verification
Sapico (1980, 1984)[190,191]	Evaluation of deep-tissue microbiology in people with diabetic foot infection using different sampling techniques (ulcer swab pre- and post-amputation, curettage and needle aspiration)	Some patients did not have foot ulceration; no diagnostic verification for detection of wound infection
Schneider (1983)[192]	Comparison of two methods of tissue sampling (single tissue sample divided into 4 specimens versus tissue samples taken from 4 separate areas of the wound) in pressure sores and infected surgical wounds	2×2 diagnostic data not available
Sharp (1979)[193]	Comparison of cultures taken at the bedside with those obtained via surgical dissection at the infection site in patients undergoing a surgical procedure for infected DFUs	2×2 diagnostic data not available

[a] A number of other studies focusing on the prevalence and sensitivities of microorganisms, and the diagnosis of osteomyelitis, were identified through the diagnostic search strategy, but have not been listed here.

Summary of excluded effectiveness studies

Study	Description	Reason for exclusion
Acevedo (1990)[194]	Antibiotics infused into limb with tourniquet vs conventional systemic antibiotics	Failed to meet study design inclusion criteria
Akova (1996)[195]	Prospective follow-up of patients treated with parenteral S/A	No comparison of interventions
Anon (1992)[196]	Guidelines for diabetic foot care	No comparison of interventions
Anon (1996)[197]	Guidelines for diabetic foot care	No comparison of interventions
Apelqvist (1989)[198]	Wound classification	No comparison of interventions
Armstrong (1997)[199]	Risk factors associated with puncture wounds in diabetics vs non-diabetics	No comparison of interventions
Armstrong (1997)[200]	Retrospective case survey of seasonal variation in lower extremity amputation	No comparison of interventions
Beam (1989)[201]	CCT of oral vs intravenous ciprofloxacin	Not DFU patients
Bendy (1965)[202]	RCT of standard therapy vs standard therapy plus topical gentamicin cream	Not DFU patients
Bonham (2001)[203]	Systematic review of antibiotic treatment for osteomyelitis	Focus on osteomyelitis
Bose (1979)[204]	Case series study of surgical approach to treatment	Failed to meet study design inclusion criteria. No data by ulcer group
Bowering (2001)[205]	Non systematic overview of DFU aetiology, assessment and treatments	Failed to meet study design inclusion criteria
Boxer (1969)[206]	RCT of collagenase vs placebo in patients with venous, arterial or pressure ulcers	Not DFU patients
Brill (2000)[207]	CCT of HBO_2 vs standard care	No antimicrobial intervention
Brunner (1999)[208]	Overview of microbiology and antimicrobial treatments for diabetic foot infection	Failed to meet study design inclusion criteria
Calhoun (1988)[209]	Retrospective evaluation of Wagner classification protocol	No comparison of interventions
Cappelli (1969)[210]	Uncontrolled study (Italian)	Failed to meet study design inclusion criteria. Not DFU patients
Chapuis (1964)[211]	Uncontrolled study (French)	Failed to meet study design inclusion criteria
Close-Tweedie (2001)[212]	Povidone-iodine in podiatric wounds	Failed to meet study design/intervention inclusion criteria
Collier (1997)[213]	Correspondence regarding compression and venous leg ulcers	Failed to meet study design/intervention inclusion criteria
Combe (1999)[214]	Non-systematic overview of assessment and treatment of diabetic feet	Failed to meet study design criteria
Cunha (2000)[215]	Non-systematic overview of diabetic foot infection	Failed to meet study design criteria
Danziger (1988)[216]	RCT of imipenem vs gentamicin/clindamycin	Insufficient number of DFU patients and data on foot ulcer patients not presented separately
Davies (1982)[217]	RCT of augmentin vs co-trimoxazole	No data presented for infected DFUs
Degreef (1998)[218]	Non-systematic overview	Failed to meet study design inclusion criteria. Not specific to DFUs
Dereume (1985)[219]	Survey of yeast culture from leg ulcers and risk factors for yeast infection	Failed to meet study design/intervention inclusion criteria

continued

Study	Description	Reason for exclusion
Dillon (1990)[220]	Case series study of local antibiotic injections and end-diastolic compression boot	Failed to meet study design inclusion criteria
Dominguez (1989)[221]	RCT of intravenous/oral ciprofloxacin vs intravenous ceftazidime	No data for DFUs
Donaghue (1998)[222]	RCT of collagen–alginate dressing vs saline gauze	Failed to meet intervention inclusion criteria
Draszkiewicz (1992)[223]	Report on diabetic foot care	Failed to meet study design inclusion criteria
Edmonds (2001)[224]	Pathophysiology of the diabetic foot	Failed to meet study design inclusion criteria. No comparison of interventions
Edmonds (2000)[225]	Non-systematic overview of novel treatments for DFUs	Failed to meet study design inclusion criteria
Faglia (1996)[226]	RCT of hyperbaric oxygen therapy vs standard treatment	Failed to meet intervention inclusion criteria as not an antimicrobial intervention
Fass (1989)[227]	RCT of intravenous/oral ciprofloxacin vs ceftadime	Insufficient number of DFU patients and data on foot ulcer patients not presented separately
Fejfarova (2002)[228]	Microbiological resistance as risk factor for amputation	Failed to meet study design/intervention inclusion criteria
Fernandez Montequin (1991)[229]	CCT of antimicrobial interventions in diabetic amputees	Not DFU patients
File (1983)[230]	RCT of amdinocillin plus cefoxitin vs cefoxitin	Insufficient numbers of diabetic patients. Unclear as to how many patients had foot ulcers
File (1991)[231]	Non-systematic overview of T/C therapy	Failed to meet study design inclusion criteria
File (1991)[232]	Overview of treatments for bacterial skin/soft tissue infections	Failed to meet study design/intervention inclusion criteria
File (1994)[233]	Overview of trials of piperacillin/tazobactam	Failed to meet study design inclusion criteria
Foster (2001)[234]	Overview of diabetic foot management	Failed to meet study design inclusion criteria. No comparison of interventions
Foster (2001)[235]	Overview of diabetic foot management	Failed to meet study design inclusion criteria. No comparison of interventions
Frykberg (2000)[79]	Clinical guidelines	No comparison of interventions
Fuentes Sermeño (2001)[236]	Evaluation of oral levofloxacin vs ciprofloxacin	Not DFU patients
Gentry (1989)[237]	RCT of oral ciprofloxacin vs parenteral cefotaxime	Not clear whether DFU patients
Gentry (1991)[238]	RCT of ofloxacin vs parenteral therapy for osteomyelitis	Not DFU patients
Gentry (1992)[239]	Overview of lactam and quinolone agents for skin/skin structure infections	Failed to meet study design inclusion criteria
Gentry (1993)[240]	Diagnosis and management of DFU	No comparison of interventions
Gentry (1989)[241]	RCT of oral ofloxacin vs intravenous cefotaxime	Not clear whether DFU patients
Goldenheim (1995)[242]	Correspondence	Failed to meet study design inclusion criteria
Gomez (1992)[243]	Risk factors for diabetic foot infection	Failed to meet study design/intervention inclusion criteria
Gomis (1990)[244]	Uncontrolled case series study of antimicrobial therapy	Failed to meet study design inclusion criteria
Grayson (1995)[245]	Non-systematic overview of diabetic foot infection and antimicrobial treatment	Failed to meet study design inclusion criteria
Hanft (2002)[246]	RCT of Dermagraft vs standard care	Failed to meet intervention inclusion criteria

continued

Study	Description	Reason for exclusion
Hart (1996)[247]	Non-systematic overview of β-lactamase inhibitors	Failed to meet study design inclusion criteria
Hartemann-Heurtier (2000)[248]	Non-systematic review of antibiotics used with diabetic foot patients	Failed to meet study design inclusion criteria
Helaly (1988)[249]	RCT/CCT of enzyme applications	Failed to meet intervention inclusion criteria. Unclear whether DFU patients
Henyk (1999)[250]	CCT of sea buckthorn ointment	Failed to meet intervention inclusion criteria
Hodges (1986)[251]	Non-systematic overview of diabetic foot management	Failed to meet study design inclusion criteria
Hughes (1987)[45]	RCT of cefoxitin vs ceftizoxime	Not all patients diabetic and not clear how many had a foot ulcer
Huizinga (1986)[252]	RCT/CCT of antibiotic prophylaxis	Insufficient number of diabetic patients and data on DFU patients not presented separately
Ignacio (1984)[253]	Uncontrolled case series study of hyberbaric oxygen therapy	Failed to meet study design/intervention inclusion criteria
Jamil (2001)[254,255]	Uncontrolled case series on management of diabetic foot infections	Failed to meet study design/intervention inclusion criteria
Jensen (1998)[256]	RCT of moist wound dressing protocols	Failed to meet intervention inclusion criteria as not an antimicrobial intervention. Infected ulcer patients excluded
Johnson (1985)[257]	Evaluation of ticarcillin plus clavulanic acid	No comparison of interventions. No separate data for DFU patients
Joseph (1990)[258]	Non-systematic overview of diabetic foot infection	Failed to meet study design criteria
Joseph (1987)[259]	Non systematic overview of physiopathology in the diabetic foot	Failed to meet study design criteria
Joseph (1987)[260]	Puncture wound infections	Failed to meet patient inclusion criteria
Kacy (1982)[261]	Uncontrolled case series of amputation in diabetic/non-diabetic patients	Failed to meet study design/intervention inclusion criteria
Kaltenthaler (1998)[98]	Systematic review of antimicrobial agents for DFU	Used for reference purposes only
Karchmer (1999)[262]	Overview of fluroquinolones	Failed to meet study design/intervention inclusion criteria
Karsegard (1995)[263]	Non-systematic overview of antibiotic therapy for diabetic foot infection	Failed to meet study design inclusion criteria
Kaufman (1994)[264]	Non-systematic review on prevention of DFUs	Failed to meet study design inclusion criteria
Kerstein (1997)[265]	Retrospective case review of toe amputation in diabetic patients	Failed to meet study design inclusion criteria
Klepser (1997)[266]	RCT of piperacillin/tazobactam vs ticarcillin/clavulanate vs ampicillin/sulbactam	Not DFU patients
Koveker (2000)[267]	Review of growth factors in wound repair	Failed to meet study design/intervention inclusion criteria
Krikava (1999)[268]	Survey of isolates and sensitivity to antibiotics in diabetic feet	Not clear whether DFU patients
Laing (1994)[269]	Non systematic overview of DFU management	Failed to meet study design inclusion criteria
Larsson (1995)[270]	Review of amputation rates, costs and prevention	Failed to meet study inclusion/intervention inclusion criteria
Lee (1997)[271]	Case series study of diabetic foot patients receiving hyperbaric oxygen therapy	Failed to meet study inclusion/intervention inclusion criteria
LeFrock (1983)[272]	Evaluation of cefoxitin in diabetic patients with lower extremity infections	Failed to meet study design criteria: as no control/comparison group

continued

Study	Description	Reason for exclusion
Lentino (1991)[273]	Evaluation of oral and intravenous ofloxacin	Not clear whether DFU patients
Lipsky (1997)[46]	RCT of intravenous ofloxacin followed by oral ofloxacin vs intravenous ampicillin/sulbactam followed by oral amoxicillin/clavulanate	Insufficient number of DFU patients and data on foot ulcer patients not presented separately
Loffler (1986)[274]	RCT of sulbactam plus ampicillin vs cefotaxime	Insufficient number of DFU patients and data on foot ulcer patients not presented separately
Madsen (1996,1998)[275,276]	RCT comparing oral and intravenous penicillin vs no treatment	Insufficient number of diabetic patients and data on foot ulcer patients not presented separately
Mason (1999)[99,277]	Systematic review addressing different methods of treating DFU	For reference purposes only
Mayer (1993)[278]	Non-systematic review of povidone-iodine wound healing products	Failed to meet study design inclusion criteria
Mizel (1989) [279]	Non-systematic overview of diabetic foot infection	Failed to meet study design inclusion criteria
Motarjeme (1993)[280]	Retrospective study of thrombolysoangioplasty as an alternative to amputation	Not clear whether DPU patients
Murphy (1981)[281]	Non-systematic overview of diabetic foot infections	Failed to meet study design inclusion criteria
Nichols (1997)[282]	RCT of levofloxacin vs ciprofloxacin	Unable to identify data for DFU patients
Ohsawa (2001)[283]	Case series study of amputation outcomes in diabetic foot patients	Failed to meet study design inclusion criteria. No comparison of interventions.
Parish (1993) [284]	RCT of fleroxacin vs. ceftazidime	Not clear whether DFU patients
Parish (1984) [285]	CCT of augmentin vs cefaclor	No data on DFU infections
Parish (1984) [285]	RCT of ceftizoxime vs cefamandole	Not DFU patients
Parish (1987)[286]	RCT of cefuroxime axetil vs cefaclor	Insufficient number of DFU patients and data on foot ulcer patients not presented separately
Partsch (1993)[287]	RCT of intravenous pressure infusions containing radioactive tracers	No comparison of antimicrobial interventions
Pepe (1999)[288]	RCT of ASA, Ginko Biloba extract, arginine plus magnesium vs ASA plus conventional haemorrheology	No comparison of antimicrobial interventions
Perez-Ruvalcaba (1987)[289]	RCT of ciprofloxacin vs cefotaxime	No data for DFU patients
Peters (2001)[290]	RCT of electrical stimulation vs placebo	No comparison of antimicrobial interventions
Pien (1983)[291]	CCT of two dosage regimens of Cefaclor and amoxicillin/clavulanic acid	No data for DFU patients
Pinzur (1993)[292]	Non-systematic overview of amputation level selection in the diabetic foot patient	Failed to meet study design inclusion criteria. No comparison of antimicrobial interventions
Pinzur (1999)[293]	Summary of guidelines for diabetic foot care	Failed to meet study design/intervention inclusion criteria
Pitkin (1995)[294]	Comparison of meropenem with other agents in skin/soft tissue infections	Failed to meet study design inclusion criteria. No data by wound type
Powers (1993)[295]	RCT of oral fleroxacin vs A/C	No data on DFU patients
Real (2001)[296]	Prospective cohort study of risk factors for hospitalisation	Failed to meet study design inclusion criteria. No comparison of interventions

continued

Study	Description	Reason for exclusion
Rice (2001)[297]	RCT of biofeedback-assisted relaxation vs relaxation	No comparison of antimicrobial interventions
Rittenhouse (1996)[298]	CCT of zinc–saline wet dressings vs normal saline wet dressings	No comparison of antimicrobial interventions
Saltzman (1999)[299]	Non-systematic review of diabetic foot infection	Failed to meet study design inclusion criteria
Sauerwein (1994)[300]	Commentary on antibiotic treatments relating to DFUs	Failed to meet study design inclusion criteria
Schwegler (2002)[301]	Overview of diabetic foot management	Failed to meet study design inclusion criteria
Seewald (1999)[302]	Non-systematic overview of microbiological aspects of the diabetic foot	Failed to meet study design inclusion criteria
Segev (1990)[303]	RCT of pefloxacin vs ceftazidime	Insufficient number of patients with diabetes and not clear how many had an ulcer
Self (1987)[304]	RCT of ciprofloxacin vs cefotaxime	No data on DFU patients
Senneville (2002)[305]	Case series study of rifampicin and fluoroquinolone	Failed to meet study design inclusion criteria
Sesin (1990)[306]	Case series study of oral clindamycin and ciprofloxacin	Failed to meet study design inclusion criteria
Siami (2001, 2002)[307,308]	RCT of clinafloxacin vs piperacillin/tazobactam	Not DFU patients
Sibbald (2001)[309]	Case series study of ionised nanocrystalline silver dressing in chronic wound care	Failed to meet study design inclusion criteria
Siebert (1985)[310]	RCT of ticarcillin plus clavulanic acid vs moxalactam	Not clear whether DFU patients
Smith (1996)[311]	Overview of soft tissue and diabetic foot infections	Failed to meet study design inclusion criteria
Smith (2001)[312]	Protocol description on debridement of DFUs	Failed to meet study design/intervention inclusion criteria
Steed (1992)[313]	RCT of topical CT-102 activated platelet supernatant vs placebo	Failed to meet intervention inclusion criteria as not an antimicrobial intervention
Storm (1994)[314]	Correspondence regarding analysis of tissue concentration of cefuroxime	Failed to meet study design inclusion criteria. Not clear whether all patients had ulcers
Stromberg (1986)[315]	RCT of sulbactam and ampicillin vs clindamycin and tobramycin	Not clear whether diabetic foot ulcer patients
Sussman (1992)[316]	Non-systematic review of diabetic foot problems	Failed to meet study design inclusion criteria
Tammelin (1998)[317]	Case series study of flora, antimicrobial resistance and treatment	Failed to meet study design inclusion criteria
Tan (1985)[318]	Comparison of timentin vs moxalactam	Insufficient number of DFU patients and data on foot ulcer patients not presented separately No outcome data
Tan (1996)[319]	Retrospective case review of intravenous antibiotics vs surgery plus intravenous antibiotics	Failed to meet study design inclusion criteria
Tannenbaum (1992)[320]	Case series study of venous bypass grafting	Failed to meet study design/intervention inclusion criteria
Tassler (1993)[321]	RCT of oral fleroxacin vs A/C	Not clear whether DFU patients
Tassler (1993)[322]	Non-comparative study of piperacillin/tazobactam	Failed to meet study design inclusion criteria
Temple (2000)[323]	Semi-systematic review of antibiotic treatments for DFUs	Failed to meet study design inclusion criteria
van de Meer (1996)[324]	Overview of antibiotic treatments for diabetic foot infection	Failed to meet study design inclusion criteria

continued

Study	Description	Reason for exclusion
Vanscheidt (2002)[325]	RCT of Butcher's broom extract vs placebo	Failed to meet intervention inclusion criteria as not an antimicrobial intervention
Wheatley (2001)[326]	Audit protocol relating to diabetic foot ulcers	Failed to meet study design/intervention inclusion criteria
Young (1995)[327]	Measurement of metatarsal pressure using plantar ultrasound	Failed to meet study design/intervention inclusion criteria
Zlatkin (1987)[328]	Non-systematic overview of diabetic foot management	Failed to meet study design inclusion criteria

Summary of excluded cost-effectiveness studies

Study	Description	Reason for exclusion
Bentkover (1993)[329]	Cost-effectiveness analysis of thrombin induced platelet releasate versus saline solution to treat DFUs	Focus is not management of infection in DFUs
Apelqvist (1994,1995)[131,137,138]	Cost analysis of primary healing and healing with amputation in DFUs	No synthesis of costs and benefits (costs only)
Eckman (1995)[15]	Markov model used to estimate the cost-effectiveness of different aspects of the diagnosis and treatment of diabetic patients with foot infections and suspected osteomyelitis	Focus is management of osteomyelitis rather than wound infection
Morrison (1995)[330]	Evaluation of the sensitivity, specificity, clinical utility and cost-effectiveness of magnetic resonance imaging in the diagnosis of osteomyelitis of the foot in diabetics	Focus is diagnosis of osteomyelitis rather than wound infection; 56% of feet studied were not diabetic; magnetic resonance imaging was not compared directly with a reference standard

Appendix 7

Experts' views on definition and management of clinically infected diabetic foot ulcers

	A: secondary referral centre (DGH with diabetes centre), England	B: tertiary referral centre in England (works closely with a bone infection team)	C: secondary referral centre in England	D: tertiary referral centre, Wales	E: tertiary referral centre, Canada	F: tertiary referral centre, England
Question ↓	**Podiatrist**	**Podiatrist**	**Vascular surgeon**	**Nurse specialist**	**Medical doctor**	**Diabetologist**
A. Diagnosis of infection						
1. In general, what set of criteria would you say is used to diagnose clinically an infected foot ulcer?	Swelling, red colour, smell and pain If there are 2 of these signs then she acts on them; if there is only 1 sign she takes a swab	Redness, pain, induration, discharge, heat, swelling, smell. If cellulitis less than 2 cm from the entry point of infection, likely to be a minor infection. If extensive cellulitis, likely to be moderate or severe infection They often do an X-ray, or blood test/temperature to see if pyrexial	Surrounding cellulitis, presence of undermining, oedema, failure to heal when you thought it should (changes in plain X-ray overtime, MRI – increasing tissue oedema) "We don't use swabs to diagnose infection, the clinical impression is the diagnosis, swabs simply confirm the organism"	Presence of undermining, excessive or malodorous exudate, pain, pus, spreading cellulitis, bleeding wound bed, cellulitis around the wound, probe to bone With the exception of probe to bone, for all the others 1 factor = high suspicion, presence of 2 factors = definitive	Pain in a painless foot (a neuropathic foot) Swelling above the foot Increased exudate since last week, Probe to bone, X-ray ESR>65 CRP > 30 Difference in 4–5 degrees as measured by thermometry	Purulent discharge, erythema, warmth, swelling. Also more subtle signs – change in both ulcer base and colour; increase in exudate volume
B. Incidence of clinically diagnosed infection						
2. Out of 10 consecutive outpatients with diabetic foot ulcers, how many of them will fulfil the set of criteria you outlined in the previous question?	3/10	> 5/10 Remarks they are a specialist centre	1/10 out-patients 10/10 in-patients (infection is a key reason for admission)	4 or 5/10 4 would get oral AB 1 would get IV AB (if person is 'unwell, if ulcer can probe to bone, or there is out of control diabetes, spreading infection')	5 or 6/10 The longer the ulcer has been there the more likely the ulcer is infected; the deeper the ulcer, the higher chance of infection. With poor diabetic control, there is likely to be infection. Also, poor control is a symptom of infection	4 or 5/10

continued

Question ↓	A: secondary referral centre (DGH with diabetes centre), England Podiatrist	B: tertiary referral centre in England (works closely with a bone infection team) Podiatrist	C: secondary referral centre in England Vascular surgeon	D: tertiary referral centre, Wales Nurse specialist	E: tertiary referral centre, Canada Medical doctor	F: tertiary referral centre, England Diabetologist
C. Alternative courses of action						
3. Out of 10 consecutive outpatients initially diagnosed with a clinically infected DFU (according to the set of criteria you described in question one), how many of these will commence a course of oral systemic antibiotics without a formal diagnostic test having taken place?	All of them	Majority go onto empirical therapy	Virtually all of them, because infection so easily becomes a plantar space infection. Once you have diagnosed infection, you treat until otherwise proven	All of them would get antibiotics immediately. The consequences of failing to act are serious – so not left to chance	5 to 7/10 Higher risk of harm if you wait	All of them
4. What patient, foot or ulcer characteristics prompt you to prescribe oral systemic antibiotics to commence immediately?	All patients get antibiotics so not relevant	Practically all would get antibiotics immediately: only patients with high suspicion of osteomyelitis and not at risk of systemic infection would get a bone biopsy before having any antibiotics NB: day of week also important – on a Friday they give antibiotics for a superficial looking redness/infection, whereas Monday–Thursday they would bring patient back and see progress before starting with antibiotics (and do so only if redness increasing)	See above – they all get antibiotics	See above – they all get antibiotics	Limb-threatening infection See the infection criteria above	

continued

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Question ↓	**Podiatrist**	**Podiatrist**	**Vascular surgeon**	**Nurse specialist**	**Medical doctor**	**Diabetologist**
5. How many of the same 10 patients will be formally tested using one or more formal diagnostic tests for infection, i.e. wound biopsy, wound swab, X-ray, among others, and receive no systemic antibiotics until the results of the formal test are obtained?	1 or 2/10	People with suspected osteomyelitis	None	None	3 to 5/10. They would be debrided, treated with local cadexomer iodine or silver, and then reassessed in 2 weeks	No reply
6. Which diagnostic test would you most commonly use?	Swab	Deep tissue biopsy after debridement Probe to bone	Swab	Swab (their laboratory cannot deal with biopsy specimens very well)	Swab	Neuropathic ulcers would be scraped for a sample Neuro-ischaemic ulcer would be swabbed. (7/10 ulcers are neuropathic)

continued

Question ↓	A: secondary referral centre (DGH with diabetes centre), England **Podiatrist**	B: tertiary referral centre in England (works closely with a bone infection team) **Podiatrist**	C: secondary referral centre in England **Vascular surgeon**	D: tertiary referral centre, Wales **Nurse specialist**	E: tertiary referral centre, Canada **Medical doctor**	F: tertiary referral centre, England **Diabetologist**
7. If an initial diagnostic test proved uninformative and the ulcer still appeared infected, would you repeat the same test, OR would you use a different test (e.g. would you repeat a wound swab, or would you use a wound biopsy to get a better sample?). Please list the options you would use in the order you would use them	Act on the symptoms not the swab Might reswab	Debride ulcer again and take biopsy again	Depends on who took 1st swab; if it was him, reswab and request MRI scan. If it was another clinician, he would swab and wait (biopsy is not particularly useful)	Might curettage the wound. If the probe to bone revealed a chunk of bone, they would pick that out and send it off for microbiology MRI scans take too long to get in their setting Might take an X-ray if the patient has not had one in a while	Reswab, then biopsy	Deeper sample required if neuropathic ulcer
8. What patient, foot or ulcer characteristics prompted you to use a formal diagnostic test?	If only one of the characteristics of infection present				If I were planning to use a skin substitute, then I would want to check the wound bed was 'sterile' before using the really expensive skin	

continued

	A: secondary referral centre (DGH with diabetes centre), England	B: tertiary referral centre in England (works closely with a bone infection team)	C: secondary referral centre in England	D: tertiary referral centre, Wales	E: tertiary referral centre, Canada	F: tertiary referral centre, England
Question ↓	**Podiatrist**	**Podiatrist**	**Vascular surgeon**	**Nurse specialist**	**Medical doctor**	**Diabetologist**
9. How many of these same 10 patients will neither be treated with systemic antibiotics or performed a diagnostic test?	Up to 1/10 would be treated with topical agents	Small proportion	Less than 1/10. There are patients with infection but the treatment they need is surgery (e.g. ischaemic). One approach is to mummify the infection with topical antimicrobials and pulse doses of antibiotics	None – the consequences too dire (leg- and life threatening)	None	None
10. What patient, foot or ulcer characteristics prompt you to continue with current management of these DFUs?	Prolonged presence of just one sign	Monday morning – patient looks well, normal CRP and ESR	Old. Frail and very ill anyway			
11. How long would you continue with your current management of these DFUs before making a change?	14 days		Depends on the patient			
D. The 'uninfected', static ulcer						
12. How long would you continue with the standard treatment before making a change?	4 weeks	6–8 weeks Need to check if pressure is really being offloaded and if arterial supply is really OK	If it is slowly improving, never swab. They have a 'pathway' – an impression of how an ulcer proceeds, and only swab if it deviates from this	There is no time guide	Uses the Margolis criteria (there should be a 30% reduction in area by week 4)	3–4 weeks

continued

	A: secondary referral centre (DGH with diabetes centre), England	B: tertiary referral centre in England (works closely with a bone infection team)	C: secondary referral centre in England	D: tertiary referral centre, Wales	E: tertiary referral centre, Canada	F: tertiary referral centre, England
Question ↓	**Podiatrist**	**Podiatrist**	**Vascular surgeon**	**Nurse specialist**	**Medical doctor**	**Diabetologist**
13. How many of these patients (out of 10 consecutive) will commence a course of oral systemic antibiotics without a formal diagnostic test having taken place?	None. Swab first and then depending on the results give antibiotics	Negligible Other treatments include silver/iodine dressings, removal of slough	Negligible – virtually all would be sampled. As the choice of antibiotics in these people depends totally on the bacteria present		0/10 (He would swab all 10 (**before** using an antibiotic) and give topical antimicrobials while deciding what to do	None – he would swab and if a bacterial report comes back as +++, then he would treat
14. What patient, foot or ulcer characteristics prompted you to prescribe oral systemic antibiotics to commence immediately?	None	A very longstanding wound	See above	If the person's diabetic control appears to be deteriorating – then consider infection as the cause		None – he would not
15. How many of the same 10 patients will be formally tested using one or more formal diagnostic tests for infection, i.e. wound biopsy, wound swab, X-ray, among others, and receive no systemic antibiotics until the results of the formal test are obtained?	10/10	10/10	10/10	Reassess with a higher index of suspicion, 1. X-ray 2. MRI (ask local radiographer for advice on imaging)	10/10	10/10 Neuropathic = curettage Neuro/ischaemic = swab

continued

Question ↓	A: secondary referral centre (DGH with diabetes centre), England **Podiatrist**	B: tertiary referral centre in England (works closely with a bone infection team) **Podiatrist**	C: secondary referral centre in England **Vascular surgeon**	D: tertiary referral centre, Wales **Nurse specialist**	E: tertiary referral centre, Canada **Medical doctor**	F: tertiary referral centre, England **Diabetologist**
16. Which diagnostic test would you most commonly use?	Swab	Biopsy	Swab			
17. If an initial diagnostic test proved uninformative and the ulcer still appeared infected, would you repeat the same test, OR would you use a different test (e.g. would you repeat a wound swab, or would you use a wound biopsy to get a better sample?). Please list the options you would use in the order you would use them	Biopsy (particularly if you suspect viral infection)	Bone biopsy MRI	Reswab after a few weeks Might also do an X-ray and MRI scan – partly to inform assessment of progress, also to plan surgery, AND to persuade patient that something is happening in their foot (a walking time bomb)			

continued

Question ↓	A: secondary referral centre (DGH with diabetes centre), England Podiatrist	B: tertiary referral centre in England (works closely with a bone infection team) Podiatrist	C: secondary referral centre in England Vascular surgeon	D: tertiary referral centre, Wales Nurse specialist	E: tertiary referral centre, Canada Medical doctor	F: tertiary referral centre, England Diabetologist
E. Definition of clinical infection						
18. One author has used the following definition of clinical infection in diabetic foot ulceration, 'erythema, induration and discharge' (Caputo, 2000).[25] Are there any elements of this definition that you disregard when assessing DFUs?	All are OK	Include them all NB: redness and pain may come from a Charcot foot, not infection (need to X-ray to exclude bone changes)	Induration: because of the modified response to neuropathy, the sympathetic response means that swelling does not always equal infection. Erythema: important, but in severe neuropathy lack of erythema does not mean lack of infection. Discharge: not useful – if you already see pus discharge you are too late! Need to assess continually the volume and characteristics of discharge and act if there is a change in these	All appear relevant	All appear relevant. Also uses erythema greater than 2 cm around margin of ulcer. Probe to bone is enough on its own to equal infection, OR the presence of at least 2 signs	Would not drop any

continued

Question ↓	A: secondary referral centre (DGH with diabetes centre), England **Podiatrist**	B: tertiary referral centre in England (works closely with a bone infection team) **Podiatrist**	C: secondary referral centre in England **Vascular surgeon**	D: tertiary referral centre, Wales **Nurse specialist**	E: tertiary referral centre, Canada **Medical doctor**	F: tertiary referral centre, England **Diabetologist**
Other information						
19. What is the local choice of first line antibiotics for empirical therapy?			Ciprofloxacin, clindamycin and metronidazole (they all have equal tissue penetration whether given oral or i.v.) – inpatients get i.v., outpatients get oral		Clindamycin and ciprofloxacin	Inpatients get amoxicillin (for the strep.), flucloxacillin (for the staph.), and metronidazole for the anaerobes and ceftazidime for the Gram negatives Outpatients get different regimen depending on severity of infection. Superficial: amoxicillin and flucloxacillin Deep: Amoxicillin + flucloxacillin + metronidazole + ciproxin

continued

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Question ↓	**Podiatrist**	**Podiatrist**	**Vascular surgeon**	**Nurse specialist**	**Medical doctor**	**Diabetologist**
20. Other information		They debride the ulcers down to a good base Patients with apparently superficial infection get flucloxacillin. Patients with more extensive/severe may get biopsies and change antibiotics on that basis NB: osteomyelitis and soft tissue infections treated in different ways – you must have a definitive culture to get the osteomyelitis treated properly. Toes sometimes respond to empirical therapy – back foot bones do not	Once assessed as infected – swab and start local 'empirical therapy' immediately. Reassess the appropriateness of the antibiotic given in the light of both a 24 and a 72-hour swab result from laboratory When bone is infected the course of antibiotics lasts for 3 months		Standard care must have vascular correction where possible, control of infection and pressure off loading You need a good swabbing technique Thinks laboratory results should be at least semi-quantitative You must sample everything at baseline assessment of infection because if the local 'empirical therapy' does not work then you can tailor next dose A swab does not diagnose infection – the clinician does that. Infection = dose/host response You do not treat the swab, you treat the patient They surveyed 100 people with neuropathic foot ulcers – 60% had had antibiotics in the last 6 months Stated 'a local swab mirrors the bacteria sampled from a deeper biopsy' Mentioned critical colonisation – the wound does not look infected but is failing to improve, so it must be infected	

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We look forward to hearing from you.

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