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REVIEW ARTICLE

A systematic review of the effectiveness of interventions in the management of infection in the diabetic foot†

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Summary

The International Working Group on the Diabetic Foot expert panel on infection conducted a systematic review of the published evidence relating to treatment of foot infection in diabetes. Our search of the literature published prior to August 2010 identified 7517 articles, 29 of which fulfilled predefined criteria for detailed data extraction. Four additional eligible papers were identified from other sources. Of the total of 33 studies, 29 were randomized controlled trials, and four were cohort studies.

Among 12 studies comparing different antibiotic regimens in the management of skin and soft-tissue infection, none reported a better response with any particular regimen. Of seven studies that compared antibiotic regimens in patients with infection involving both soft tissue and bone, one reported a better clinical outcome in those treated with cefoxitin compared with ampicillin/sulbactam, but the others reported no differences between treatment regimens. In two health economic analyses, there was a small saving using one regimen versus another. No published data support the superiority of any particular route of delivery of systemic antibiotics or clarify the optimal duration of antibiotic therapy in either soft-tissue infection or osteomyelitis. In one non-randomized cohort study, the outcome of treatment of osteomyelitis was better when the antibiotic choice was based on culture of bone specimens as opposed to wound swabs, but this study was not randomized, and the results may have been affected by confounding factors.

Results from two studies suggested that early surgical intervention was associated with a significant reduction in major amputation, but the methodological quality of both was low. In two studies, the use of superoxidized water was associated with a better outcome than soap or povidone iodine, but both had a high risk of bias. Studies using granulocyte-colony stimulating factor reported mixed results. There was no improvement in infection outcomes associated with hyperbaric oxygen therapy. No benefit has been reported with any other intervention, and, overall, there are currently no trial data to justify the adoption of any particular therapeutic approach in diabetic patients with infection of either soft tissue or bone of the foot.

Keywords diabetes mellitus; diabetic foot; infection; osteomyelitis; antibiotics; surgery; systematic review

Introduction

Infection of the foot is a common complication in patients with diabetes mellitus, and it can lead to significant morbidity (including lower extremity amputation) and mortality. Several groups have developed guidelines for treating diabetic foot complications on the basis of the limited available published data. The Infectious

Diseases Society of America has developed evidence-based guidelines specifically directed at managing diabetic foot infections (DFI), but the recommendations are not based on a formal systematic review of the literature.

Two systematic reviews of some aspects of DFIs have been published. In 2008, the International Working Group on the Diabetic Foot conducted a systematic review of treatment of diabetic foot osteomyelitis [1], and in 2011 The National Institute for Health and Clinical Excellence (NICE, UK) published the results of a systematic review of the management of all aspects of care for inpatients with a diabetic foot complication [2]. The present systematic review includes an update of the 2008 osteomyelitis guideline but is extended to include all types of bacterial DFIs. This review focuses on studies of therapeutic interventions and does not cover definitions for infection, methods for diagnosis (clinical, imaging or microbiological sampling) and the interface between critical colonization and infection.

Methods

Literature search was conducted using PubMed and Embase, seeking all prospective and retrospective studies in any language that evaluated interventions for the treatment of foot infections in people aged 18 years or older with diabetes mellitus. The search strategy employed is described in Appendix A. Eligible studies included randomized controlled trials (RCTs), case–control studies, prospective and retrospective cohort studies and those of interrupted time series (ITS) or controlled before-and-after design (CBA). Uncontrolled case series, studies in which controls were historical and case reports were excluded. Studies where patients with DFIs formed part of the total population were excluded if the data for the subgroup with diabetes were not separately described.

One author assessed each identified reference by reviewing the title and abstract for potential eligibility. Full copies of potentially eligible publications were independently reviewed by two authors to determine whether they met the criteria for being included. When the two reviewers disagreed, they worked to reach consensus, sometimes with input from another reviewer. Using specially prepared forms, the reviewers noted the study design, characteristics of patient populations, type(s) of interventions, all outcomes and the duration of follow-up of included patients. Investigators scored all studies for methodological quality using scoring lists developed by the Dutch Cochrane Centre [3]. Quality items were rated as 'done', 'not done', or 'not reported', and only those rated as 'done' contributed to the methodological quality score. Equal weighting was applied to each validity criterion for every study design.

The methodological quality score was translated into a level of evidence according to the Scottish Intercollegiate Guidelines Network (SIGN) instrument as follows: (1) RCTs and (2) case–control, cohort, CBA or ITS studies. Studies were also rated as: ++ (high quality with low risk of bias), + (well conducted with low risk of bias) and − (low quality with higher risk of bias). Co-reviewers agreed on the findings from the data extraction and the evaluation of methodological quality of each paper. Extracted data were summarized in the evidence table (see Appendix B) and described on a study-by-study narrative basis. Because of the heterogeneity of study designs, interventions, follow-up and outcomes, no attempt was made to pool the results. This evidence table was compiled following collective discussions (by electronic and in-person conferences) by all members of the working party.

Results

A total of 7517 papers were identified in the initial search: 4549 in PubMed and 2968 in Embase. After reviewing the titles and abstracts and excluding duplicate citations, we selected a total of 509 papers (460 papers in English, 26 in Russian, six in Ukrainian, six in Spanish, four in German, four in French, two in Chinese and one in Bulgarian) for full paper review. Of these, 29 papers met the criteria for inclusion. All of these papers were in English except for one which was in Chinese. Four additional papers that were not identified by our search strategy were added manually [4–7]. The data of all included papers are summarized in the evidence table (See Appendix B).

Types of study

Of the 33 studies, 29 were RCTs, and four were cohort studies. Of the 29 reported RCTs, one was actually a description of two studies in one article [8]. In some reports, patients with diabetes and a foot infection formed a subgroup of a larger group of, for instance, patients with skin and soft-tissue infections; these studies were excluded if sufficient detail was not specifically provided on the diabetic foot subpopulation. Twelve studies reported on the use of antibiotics in skin and soft-tissue infection, eight on patients with DFIs including osteomyelitis, of which one study was on the use of bone biopsy [9]. Treatment with topical antiseptic agents was reported in three studies. There were two studies of the role of surgery in DFIs and two that reported on the financial costs of antibiotic use. There were four studies that investigated treatment with granulocyte-colony stimulating factor (G-CSF); one additional paper on the use of G-CSF had not been identified in the literature search because it was filed as a letter to the editor rather than as an original study. The data of this study were extracted and added to the evidence table [6]. One study on the intramuscular administration of procaine plus polyvinylpyrrolidine was included, as well as one on the use of hyperbaric oxygen therapy (HBOT).

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Individual topics

Early surgical intervention

The two papers that reported on this topic were both single-centre cohort studies of the effect of early surgery and antibiotics versus antibiotics alone in deep foot infections with and without osteomyelitis [10,11]. Both studies suggested that there was a significant reduction of major amputation, from 27% to 13% in one study [10] and 8% to 0% in the other [11], with early minor surgery. Both studies examined outcomes associated with earlier surgery and not the particular indication for operative intervention. Because of the high risk of selection bias in deciding on which patients underwent early surgery in both studies, we find it hard to draw any conclusions from these data.

Health economics

Two studies explored the cost-effectiveness of different antibiotic regimens. The first was a cost-minimization assessment comparing treatment with ertapenem versus piperacillin/tazobactam [12] and was a subgroup analysis of a larger RCT [13]. Because piperacillin/tazobactam requires a more frequent dosing schedule than ertapenem, total costs for this regimen, including those for drug preparation and administration, were higher. The difference in cost per patient per day was, however, only of the order of $6. The second study, which explored cost-effectiveness in subjects admitted to hospital with skin and soft-tissue infection, reported a total potential cost saving of $61 per subject treated with ceftriaxone and metronidazole as opposed to ticarcillin/clavulanate [14].

Topical treatment with antiseptic agents

Two small single-centre RCTs have compared topical treatment with superoxidized water with either soap or povidone iodine. One of these studies was in patients with infected diabetic foot ulcers and outcomes of interest, i.e. odour reduction, cellulitis and extent of granulation tissue, were significantly better in the group of patients treated with superoxidized water than in controls treated with another topical disinfectant [15]. Of note, there was 81% reduction in periwound cellulitis in the intervention group versus 44% reduction in the controls. The other study was non-blinded and was conducted in patients with post-surgical wounds [16]. The duration of antibiotic treatment was significantly longer in patients treated with povidone iodine compared with those treated with superoxidized water (15.8 days versus 10.1 days; $p = 0.016$). Both studies included long-term outcomes of wound healing, but neither specifically addressed the potentially negative effect of other topical disinfectants in the comparator groups. One additional study in 30 subjects compared the results of a single application of a topical antiseptic, either iodophor and rivanol, with a control group [17]. There was a significantly reduced growth of bacteria after 24 h in the iodophor group compared with either the rivanol or control group, but the short follow-up and strictly microbiological (rather than clinical) outcome criteria limit the clinical usefulness of this study.

Granulocyte-colony stimulating factor

Four single-centre RCTs examining the adjunctive use of G-CSF in DFIs were identified [18–20]. A fifth study was published as a letter to the editor [6]. Patients had soft-tissue infection in four of the five studies and associated osteomyelitis in one [19]. In two studies, the design was double blinded; in one case the assessor was blinded, and in one only the patient was blinded. Blinding was mentioned in the fifth. In the study by Viswanathan *et al.* [6], a total of 85 patients treated with 5 μg/kg or a fixed dose (263 μg) of G-CSF were compared with 82 controls not treated with G-CSF; both groups received antibiotics and appropriate surgical wound care. Time to infection resolution was significantly lower for subjects who received G-CSF in the one study [21] but not in the others. This study [21] also reported a shorter duration of intravenous antibiotic use in G-CSF-treated patients, but this was not observed in another study [18]. Hospital length of stay was shorter for the G-CSF group in two studies [6,21] but not in a third [18]. The need for surgical intervention was not statistically different between the two groups in the three studies that examined it [6,19,21] and neither was the time to eliminate pathogens from the wound [19,21]. The results of these five studies are somewhat inconsistent and provide no clear evidence on which, if any, patients with DFIs might benefit in some clinically important way from the use of G-CSF. A meta-analysis of these five studies also concluded that adding G-CSF did not significantly affect the likelihood of resolution of infection or wound healing or the duration of systemic antibiotic therapy but was associated with a significantly reduced likelihood of lower extremity surgical interventions, including amputation and a reduced the duration of hospital stay [22].

Procaine plus polyvinylpyrrolidone

One study assessed intramuscular injection of 0.15 mL/day of procaine and polyvinylpyrrolidone for 10 days in 118 patients with a DFI affecting an ischaemic limb [23]. This observer-blinded, single-centre RCT found no significant difference between groups.

Hyperbaric oxygen therapy

Although a number of trials that have examined the effect of HBOT in patients with diabetic foot complications, including two double-blind RCTs [24,25], were found, only one study was found that specifically investigated infection as an outcome [26]. This single-centre, open label study in patients receiving standard antibiotic treatment and wound debridement compared outcomes in 15 patients who received HBOT with 15 control subjects. Although it was not explicitly stated that the subjects had a foot infection, this was implied by the use of antibiotics. There were no significant differences in the numbers of positive wound cultures, major and minor amputations or hospital stay between the intervention and control groups.

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Antibiotic choice based on bone biopsy

A single cohort study explored the effect of basing antibiotic selection on the results of culture of a bone biopsy specimen in patients with diabetic foot osteomyelitis [9]. Among 50 subjects, 32 had had previous unsuccessful treatment for osteomyelitis. The rate of remission of infection was significantly higher in the group for whom antibiotic choice was based on bone culture than in those in whom therapy was based on wound swab culture [82% vs 50%, respectively ($p = 0.02$)]. Nevertheless, it is possible that this difference was the result of confounding variables, especially the fact that patients in one of the highest enrolling centres only received a rifampicin-containing regimen if they had a bone culture.

Comparison of antibiotic regimens – skin and soft-tissue infection alone

Of the available studies comparing different antibiotic treatment regimens for skin and soft-tissue infections, 11 were RCTs, and one was a prospective cohort study [27]. Among the randomized trials, nine were multicentre studies [4,7,8,28–33], whereas two were single-centre trials [14,34]. Trial design was double blinded in three [4,8,32], investigator blinded in two [29,31] and non-blinded in six [7,14,28,30,33,34]. Three studies were subset analyses of larger trials [4,7,32]. One reported on two consecutive studies of the topical antibiotic peptide pexiganan [8]. The other studies compared systemic antimicrobial regimens: one compared two oral antibiotic regimens [34], whereas the rest involved parenteral regimens, often with a switch to oral antibiotic therapy.

The following classes of antibiotics were compared in the various studies: first, third and fifth generation cephalosporins (cephalexin, ceftriaxone and ceftobiprole, respectively); fluoroquinolones (ofloxacin, levofloxacin, ciprofloxacin and moxifloxacin); lincosamides (clindamycin); extended-spectrum penicillins plus beta lactamase inhibitors (piperacillin/tazobactam, ticarcillin/clavulanate, amoxicillin/clavulanate); carbapenems (ertapenem); nitroimidazoles (metronidazole); lipopeptides (daptomycin); and glycopeptides (vancomycin). Each of these antibiotic agents (except ceftobiprole) is widely used.

The mean duration of administration of antibiotic in patients with skin and soft-tissue infection in the two studies that reported on this ranged from 6 to 27 days [8,14]. In the study of oral regimens, the duration of administration was only 2 weeks, although three patients were actually treated for longer [34]. No differences between the regimens were observed in the ten studies with regard to infection outcome, duration of hospital admission or rates of amputation. Clinical cure rates in all studies without osteomyelitis ranged from 48% [29] to 90% [8]. One RCT of mildly infected diabetic foot ulcers reported that a topical antibiotic, pexiganan, was similar in clinical and microbiological effectiveness to an oral fluoroquinolone, ofloxacin, with fewer adverse effects [8]. No study demonstrated a significant benefit for any specific antibiotic agent, route of administration or duration of treatment.

Comparison of antibiotic regimens – studies including patients with osteomyelitis

In addition to the previously mentioned cohort study of the use of bone biopsy in patients with osteomyelitis [9], there were seven studies of antibiotic treatment of DFI in which a proportion the patients had infection of underlying bone [5,13,35–39]. The other seven studies were RCTs: three were double blind, one was single blind, three were open label, four were multicentre, and three were single-centre trials. The prevalence of osteomyelitis varied from 6% [8,13,29,36] to 81% [5]. The antibiotic classes compared in these studies were as follows: penicillins plus beta lactamase inhibitors (parenteral ampicillin/sulbactam and oral amoxicillin/clavulanate); extended-spectrum penicillins plus beta lactamase inhibitors (piperacillin/tazobactam); carbapenems (imipenem/cilastatin, ertapenem); second generation cephalosporins (cefoxitin); fluoroquinolones (ofloxacin, moxifloxacin); and oxazolidinones (linezolid).

Outcomes investigated included clinical cure [5,13,36–39], adverse drug reactions [5,13,37–39] and duration of antibiotic therapy [5,36]. Only one study, a comparison of ampicillin/sulbactam with cefoxitin, reported a difference in clinical and microbiological outcomes [35]. The clinical cure rates in this study were significantly different ($p = 0.03$) but were exceptionally low, and there were no significant differences between the groups in bacteriological response (100% vs 73%), amputations (eight in each) or duration of hospitalization (21 vs 12 days). In the other studies in which patients with osteomyelitis were included, clinical cure rates (variously defined) ranged from 61% [38] to 94% [13,39]. The mean duration of antibiotic treatment in the six studies was short, ranging from 6 days [35] to 28 days [5]. No study demonstrated a significant advantage of any particular antibiotic agent or route of administration in diabetic foot osteomyelitis.

Discussion

In planning this review, a search was made only for studies in which a treatment of DFI was compared with a contemporaneous control group, with studies being included only if at least the outcome data of the (sub)population of subjects with diabetes were reported. This led to the identification of only a very small number of suitable publications. It has to be accepted that trial design can pose problems in attempts to determine the effectiveness of different treatments in this field, and this is especially true for studies intended to evaluate the role of surgical interventions. Early surgery is accepted as essential in some cases of foot infection, and yet the trial evidence to substantiate the benefit is weak and based on just two studies – each of which had a very a high chance of bias. Another caution attaches to the use of the SIGN criteria for documenting study quality. This system ranks work mainly on the quality of study design, rather than study conduct, and this can result in apparent anomalies – with weaker studies occasionally achieving higher scores.

In most of the clinical trials that evaluated the efficacy of various antimicrobial agents, patients with DFIs were either excluded or comprised a small proportion of the study population. The design of some clinical trials allowed a *post hoc* analysis focusing on the subset of patients with a DFI, but the potential for confounding issues and the small number of subjects limits their usefulness. Not only is the number of reasonably designed studies in this field remarkably small, but most had a low score for study design, were marred by the use of small and heterogeneous populations, were poorly described or had a high risk of bias. Thus, readers should be cautious in interpreting the results of the available published work. Furthermore, circumstances dictating the choice of treatment in different countries and settings will vary according to the behaviours of affected population, nature of the presentation of infection, prevalence of different microorganisms and their antibiotic sensitivities. Selection of treatment is also severely restrained by limitation of resources in many parts of the world and poses particular problems in the management of those who live far from urban centres.

Notwithstanding the limitations, it is possible to draw several important conclusions. The reported data on skin and soft-tissue infection confirmed earlier observations suggesting that Gram-positive microorganisms play the leading role in DFI. There is, however, emerging observational evidence that Gram-negative species (especially *Pseudomonas aeruginosa*) are frequent pathogens in some populations, especially those in warm climates and developing countries [40–42]. If confirmed, this would have an important impact on the selection of antibiotic regimens. The available published data also suggest that it is possible to treat selected patients with a DFI in an outpatient setting with an oral antibiotic regimen, either initially or after a switch from parenteral therapy. The study of a topical antibiotic, pexiganan, is promising, but this agent will need to undergo further testing before it can be evaluated for approval. We identified few new data on the management of diabetic foot osteomyelitis since our relatively recent systematic review [1]. There is a great need for studies in patients with diabetic foot osteomyelitis to define the need for surgical intervention, the optimal antibiotic agents and the duration of therapy.

In the studies reported here, it was also of note that no great difference was observed in comparisons between antibiotic regimens with a relatively broad compared with a narrower spectrum of activity. It is also noteworthy that the randomized comparisons of antibiotic regimens generally reported a rather short duration of treatment (usually less than 2 weeks) – even in the few patients with bone infection– yet reported good outcomes. These observations, which conflict with most current clinical practice regarding the duration of antibiotic therapy especially in patients with osteomyelitis, need to be formally tested.

This systematic review makes clear the need for more studies on treatment of DFIs. We particularly need prospective studies that are robust, well-designed, comparative trials. These should be aimed at helping clinicians make an optimal choice of both empiric and targeted antibiotic regimens in various situations, including the choice of specific agents, the route and the duration of administration. Such studies should use a validated system for defining and classifying infections [43,44] and be designed to evaluate all relevant clinical, microbiological, financial and other outcomes for both soft-tissue and bone infections.

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Conflict of Interest

BAL has served as a consultant to Merck, Pfizer, Cubist, DiPexium, Johnson & Johnson. ARB was a Pfizer Visiting Professor in 2011 to the University of Washington Department of Allergy and Infectious Diseases, an educationally unrestricted programme for which funding was awarded to DAID on a peer reviewed and competitive basis. ARB received no personal financial benefit from this programme. ES has served as an investigator in the EU-CORE database study (NOVARTIS).

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Appendix A

Search strings for each of the sections

MEDLINE SEARCH

June 1960 to August 2010

The basic search was combined with searches for specific interventions of interest by adding the search term.

((Diabetes Mellitus OR diabetic))

AND

(((Clinical Trials) OR (comparative study) OR (epidemiologic study characteristics) OR (Clinical Trial*) OR (case-control stud*) OR (case control stud*) OR (cohort stud*) OR (Comparative stud*)))

AND

((Infection OR infected OR cellulitis OR abscess OR necrotizing fasciitis OR osteomyelitis OR gangrene OR erysipelas OR osteitis OR (Bone Diseases, Infectious) OR (Diabetic Foot)) AND (Surgery OR Amputation OR (Surgery, Plastic) OR (Preoperative Care) OR (dead space) OR drain OR hardware OR (bone samples) OR biopsy OR (Vascular Surgical Procedures) OR (Thrombolytic Therapy) OR (Costs and Cost Analysis) OR (Wound Healing) OR (Anti-Bacterial Agents) OR (Anti-Infective Agents) OR (administration and dosage) OR (Drug Administration Routes) OR parenteral OR oral OR topical OR duration OR cement OR (Methylmethacrylate) OR (Calcium Sulfate) OR implant OR collagen OR ceramic OR (Aminoglycosides OR gentamicin OR amikacin OR tobramycin) OR (Glycopeptides OR vancomycin OR Oritavancin OR dalbavancin) OR teicoplanin OR Metronidazole OR Linezolid OR (Fusidic Acid) OR Daptomycin OR Monobactam OR (Carbapenem OR imipenem OR meropenem) OR (beta-Lactams) OR (Cephalosporins) OR cefuroxime OR ceftazidime OR cephalexin OR ceftriaxone OR cefpirome OR (Clavulanic Acids) OR (Clavulanic Acid*) OR (Moxalactam) OR (Penicillins) OR penicillin OR flucloxacillin OR oxacillin OR Methicillin OR nafcillin OR ampicillin OR penicillin OR piperacillin OR (Tetracyclines) OR tetracycline OR minocycline OR doxycycline OR (Macrolides) OR erythromycin OR azithromycin OR clarithromycin OR (Lincomycin) OR clindamycin OR (Trimethoprim-Sulfamethoxazole Combination) OR cotrimoxazole OR co-trimoxazole OR (Quinolones) OR ciprofloxacin OR ofloxacin OR moxifloxacin OR levofloxacin OR (Anti-Infective Agents, Local) OR (Silver OR Silver Sulfadiazine OR iodine) OR honey OR larvae OR maggots OR larval OR (hyperbaric oxygen therapy OR hyperbaric OR (vacuum assisted wound therapy) OR (VAC therapy) OR (negative pressure therapy) OR (growth factors) OR (G-CSF) OR (granulocyte colony stimulating growth factor)))

EMBASE SEARCH

June 1960 to August 2010

The basic search was combined with searches for specific interventions of interest by adding the search term.

Map to preferred terminology (with spell check).

Also search as free text.

Include sub-terms/derivatives (explosion search).

(Diabetes Mellitus) OR diabetic

AND

(Clinical Trials) OR (comparative study) OR (epidemiologic study characteristics) OR (Clinical Trial*) OR (case-control stud*) OR (case control stud*) OR (cohort stud*) OR (Comparative stud*) OR (case control study) OR (Comparative study) OR (RCT) OR (Randomised controlled trial) OR (Costs and Cost Analysis)

AND

Infection OR infected OR cellulitis OR abscess OR (necrotizing fasciitis) OR osteomyelitis OR gangrene OR erysipelas OR osteitis OR (Bone Diseases, Infectious) OR (Diabetic Foot)

AND

(Wound Healing) OR (Anti-Bacterial Agents) OR (Anti-Infective Agents) OR (administration and dosage) OR (Drug Administration Routes) OR parenteral OR oral OR topical OR duration OR cement OR Methylmethacrylate OR (Calcium Sulfate) OR implant OR collagen OR ceramic OR Aminoglycosides OR gentamicin OR amikacin OR tobramycin OR Glycopeptides OR vancomycin OR Oritavancin OR dalbavancin OR teicoplanin OR Metronidazole OR Linezolid OR (Fusidic Acid) OR Daptomycin OR Monobactam OR Carbapenem OR imipenem OR meropenem OR (beta-Lactams) OR Cephalosporins OR cefuroxime OR ceftazidime OR cephalexin OR ceftriaxone OR cefpirome OR (Clavulanic Acids) OR (Clavulanic Acid*) OR Moxalactam OR Penicillins OR penicillin OR flucloxacillin OR oxacillin OR Methicillin OR nafcillin OR ampicillin OR penicillin OR piperacillin OR Tetracyclines OR tetracycline OR minocycline OR doxycycline OR Macrolides OR erythromycin OR azithromycin OR clarithromycin OR Lincomycin OR clindamycin OR (Trimethoprim-Sulfamethoxazole Combination) OR cotrimoxazole OR (co-trimoxazole) OR Quinolones OR ciprofloxacin OR ofloxacin OR moxifloxacin OR levofloxacin OR (Anti-Infective Agents, Local) OR Silver OR (Silver Sulfadiazine) OR iodine OR honey OR larvae OR maggots OR larval OR (hyperbaric oxygen therapy) OR hyperbaric OR (vacuum assisted wound therapy) OR (VAC therapy) OR (negative pressure therapy) OR (growth factors) OR (G-CSF) OR (granulocyte colony stimulating growth factor)

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Appendix B

Evidence tables

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
Early surgery								
Tan *et al*. [10]	Cohort Single centre Study quality, 3/8	Cohort study of 112 patients with 164 DFIs, hospitalized for treatment of the foot infection. Of these, 76 had a deep infection, 65 had osteomyelitis. No early surgery and antibiotics in 87 subjects versus early surgery and antibiotics in 77 subjects	87 infections treated without surgery in the first 3 days versus 77 treated with antibiotics + surgery (of which 46 antibiotics and debridement and 31 antibiotic and early local amputation). Duration of treatment with antibiotics unknown	Infection outcome: above ankle amputation	Amputation rate 27.6% vs 13.0% antibiotic group and antibiotic and surgical intervention groups, respectively ($p < 0.01$)	2−	No information regarding (appropriateness of) antibiotic treatment. High risk of bias as there is no assessment of severity and there is a high chance of indication bias	No sponsor identified. Provides no evidence to confirm the role of surgery, as opposed to timing of intervention
Faglia *et al*. [11]	Cohort Single centre Study quality, 5/8	Diabetes and deep foot space abscess $N = 106$, group 1: 43 subjects, group 2: 63 subjects	Group 1: immediate surgical debridement; group 2: referred from another hospital after a mean delay of 6.2 ± 7.5 days without debridement Duration of treatment with antibiotics unknown	Drainage without amputation One or more ray amputations Transmetatarsal amputation Chopart Major amputation	Group 1: 9 vs Group 2: 4 Group 1: 21 vs Group 2: 21 Group 1: 12 vs Group 2: 10 Group 1: 1 vs Group 2: 23 Group 1: 0 vs Group 2: 5 ($p < 0.001$) X^2 24.4	2−	Poor quality study despite the 5/8 score Concluded that delay in drainage increases the incidence of amputation, but this is not justified by these data because of the possibility of bias	No sponsor identified
Health economics								
Tice *et al*. [12]	RCT Subset analysis based on multicentre, double-blinded study Study quality, 6/9	99 patients with DFI, including osteomyelitis provided all infected bone was surgically removed; 56 subjects in ertapenem group vs 43 in P/T group	Substudy of SIDESTEP [13], cost-minimization assessment of ertapenem versus P/T. No duration of treatment given	Infection outcomes: Mean days of treatment Total i.v. drug doses Total antibiotic dosages Mean drug preparation and administration cost	7.6 vs 7.4 ($p = 0.8$) days of treatment, 7.5 vs 25.5 ($p < 0.0001$) total i.v. doses 8.6 vs 26.8 ($p < 0.0001$) total i.v. and oral doses, \$356 vs \$503 ($p < 0.001$) total cost of treatment for ertapenem and pip/tazo, respectively	1+	High dropout rate. Length of stay was a proxy measure. The length of stay might have been prolonged because of the trial design	Sponsored by Merck
Topical treatment with antiseptic agents								
Martínez-De Jesús *et al*. [15]	RCT Single centre Patient blinded Study quality, 4/9	Type 2 diabetes and infected, deep diabetic foot ulcers, 21 subjects	$n = 21$ intervention group: neutral pH superoxidized aqueous	Odour, periwound cellulitis and	Odour reduction was achieved in all superoxide patients (100% vs 25%;	1−	Alternate patient group allocation, yet different numbers in each group.	No sponsor identified

Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
		in intervention group vs 16 in control group	solution $n = 16$ control group: disinfectant such as soap or povidone iodine. Duration of antibiotic treatment more than 10 days	granulation tissue	$p < 0.01$) and surrounding cellulitis diminished ($p < 0.001$) in 17 patients (80.9% vs 43.7%)		Non-standardized wound classification criteria	
Chen *et al.* [17]	RCT Single centre Patient blinded Study quality, 6/9	30 patients with diabetic foot ulcers, 10 patients in each subgroup	10 diabetic foot ulcers treated with iodophor, 10 with rivanol, 10 controls One single application of topical treatment after ulcer debridement	Infection outcomes: bacteria number in wound	Number of colonies after 24 h/number of colonies at $t = 0$ was 0.961, 0.918 and 0.986 for the control group, iodophor group and rivanolol, respectively. Significantly less growth of bacteria after 24 h in the iodophor group compared with the rivanol and the control group	1+	Use of systemic antibiotics not mentioned. Study only looked at bacterial growth after 5 min and 24 h	No sponsor identified
Piaggesi *et al.* [16]	RCT Single centre Open label Study quality, 6/9	40 patients with diabetes with post-surgical wounds, who had surgery for a DFI, 20 subjects in each treatment group	Dermacyn versus povidone iodine. All patients had systemic antibiotic therapy and surgical debridement if needed. Ischaemia was an exclusion criterion Duration of treatment with P/T and metronidazol with or without teicoplanin 10.1 ± 6.1 weeks for Dermacyn and 15.8 ± 7.8 weeks for control group ($p = 0.016$). Duration of antibiotic use was an outcome measure	Infection outcomes: use of antibiotics Non-infection outcomes: Healing rate at 6 months and healing time	Duration of antibiotic use: 10.1 ± 6.1 weeks Dermacyn group vs 15.8 ± 7.8 weeks in povidone iodine group ($p = 0.016$). Healing rate at 6 months 90% in Dermacyn vs 55% in iodine group (X^2 9.9, $p = 0.002$). Healing time 10.5 ± 5.9 vs 16.5 ± 7.1, respectively ($p = 0.007$)	1+	2 patients lost to follow-up Details of the interventions and outcomes were suboptimal Possible adverse effect of iodine on wound healing not taken into account Very long antibiotic treatment period	Sponsored by Oculus Innovative Sciences
Gough *et al.* [21]	RCT Single centre Double blind Study quality, 9/9	40 patients with diabetes with moderate (International Consensus Guidelines Grade 3) infection of DFU, $n = 20$ subjects in both treatment arms	Intervention: G-CSF 5 μg/kg adjusted on basis of WCC, for 7 days versus saline control Both groups received 4 antibiotics, mean duration of i.v. antibiotics 8.5 days for G-CSF and 14.5 days for controls ($p = 0.02$)	Infection outcome measures: (1) Time to resolution of infection (2) Total time of intravenous antibiotics (3) Hospital length of stay	Intervention: 7 (5–20) days vs control: 12 (5–93) ($p = 0.03$) Intervention: 8.5 (5–30) vs control: 14.5 (8–63) days ($p = 0.02$) Intervention: 10.0 (7–31) days vs 17.5 (9–100) ($p = 0.02$) Intervention: 0 vs 4/20 (20%) ($p = 0.114$)	1++	Well-designed RCT showing significant benefit in moderate infection See meta-analysis [22] which concluded that G-CSF did not have a significant benefit with regard to either resolution of infection or healing of wounds,	Sponsored by Amgen

Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
				(4) Need for surgery (5) Time taken to eliminate pathogens from wound Non-infection outcome: (6) Effect of G-CSF on generation of neutrophil superoxide	Intervention: 4 (2–10) days vs control: 8 (2–75) days ($p = 0.02$) Intervention: 16.1 (4.2–24.2) nmol per 10^6 neutrophils/30 min vs 7.3 (2.1–11.5) ($p < 0.0001$)		although there was a significant reduction in the need for lower extremity surgery	
Yönem *et al*. [18]	RCT Single centre Blinding unknown Study quality, 2/9	15 subjects with cellulitis or Wagner 2 or less in each of the two treatment arms	15 patients treated with standard treatment (antibiotics and wound care), 15 patients treated with standard treatment + G-CSF 5 μg/kg, duration of antibiotic treatment 22.9 ± 2.0 days in G-CSF 23.3 ± 1.9 days in control group, standard treatment with G-CSF 3 days Duration of antibiotic treatment 22.9 ± 2.0 days in G-CSF 22.3 ± 1.9 days in control group	Infection outcomes: Time to resolution of infection, duration of hospitalization, duration of parenteral antibiotic administration, need for surgical intervention	No significant differences in time to resolution of infection, duration of hospitalization duration of parenteral antibiotic administration, amputation in the G-CSF treated group compared with the standard group	1−	Also includes results of respiratory burst, granulocyte count etc. Typing error in abstract ($p < 0.05$ should be $p > 0.05$)	No sponsor identified
De Lalla *et al*. [19]	RCT Single centre Observer-blinded Study quality, 6/9	Severe limb-threatening foot infection, all with osteomyelitis in diabetes $N = 40$ Patients with ABPI < 0.5 or ankle systolic pressure <50 mmHg, and patients with serum creatinine >1.6 mg/100 mL were excluded	Intervention: conventional treatment plus G-CSF 263 μg subcutaneous (s.c.) daily for 21 days versus conventional treatment (no placebo). Mean duration of antibiotics 68.9 ± 29.2 days for G-CSF patients and 58.7 ± 23.7 days for controls (not significant)	(1) Cure (complete closure of the ulcer without signs of bone infection) (2) Improvement (eradication of pathogens in addition to marked or complete reduction of cellulitis but	At 3 weeks: intervention 0 vs controls 0 At 9 weeks: intervention 7 vs controls 7 ($p = 1.0$) At 3 weeks intervention 12 vs controls 9 ($p = 0.34$) At 9 weeks: intervention 8 vs controls 4 ($p = 0.17$) At 3 weeks: intervention 8 vs controls 11 ($p = 0.34$) At 9 weeks: intervention 5 vs controls 9 ($p = 0.19$)	1+	No effect of G-CSF on eradication of infection, in contrast to [21]. Differences with [21] study relating to prevalence of osteomyelitis and choice of outcome measures	No sponsor identified

Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
		20 subjects in each treatment group		incomplete ulcer healing, or ulcer healing but persistent osteomyelitis) (3) Failure (absence of any clinical improvement) or amputation for persistent infection				
Kästenbauer *et al*. [20]	RCT Single centre Patient blinded Study quality, 7/9	Soft-tissue infection of DFU, 20 subjects in intervention group, 17 in placebo group	The patients in the intervention group received daily an initial dose of either 5 μg/kg G-CSF or placebo (0.9% sterile saline solution), s.c. Subjects were treated with i.v. antibiotics (clindamycin and ciprofloxacin) until the inflammation had visibly improved. Oral antibiotics were administered thereafter if necessary. Duration of treatment with G-CSF 10 days. Mean antibiotic treatment duration 5.6 ± 2.5 days in G-CSF group, 5.8 ± 2.3 days in placebo group	Infection outcomes: infection scores pre-treatment versus post-treatment, putrid, erythema, oedema	Patients who received G-CSF did not have an earlier resolution of clinically defined infection than placebo patients	1+	Infection score non-validated	Sponsored by Amgen No differences, like [18], whereas significant differences in resolution of signs of infection contrast with [21]
Viswanathan *et al*. [6]	RCT Single centre Double blind Study quality, Not scored	$N = 20$, with extensive cellulitis, Wagner II–III ulcers, 10 subjects in each treatment arm	The patients received daily initial dose of either 5 μg/kg body weight G-CSF or placebo (0.9% sterile saline solution), injected subcutaneously	Eradication of infection Surgery Hospital length of stay	Intervention: 9 Control: 3 (NS) Intervention: 0 Control: 3 (NS) Intervention: 7.4 Control: 8.8 ($p = 0.02$)		'Foot ulcers excluded'	Sponsored by Amgen

DOI: 10.1002/dmrr

Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
			Duration of treatment with G-CSF 10 days					
Procaine plus polyvinylpyrrolidone								
Duarte *et al*. [23]	RCT, Single centre Assessor blinded Study quality, 7/9	118 patients with ischaemic DFI, of which ischaemic gangrene $n = 63$, ischaemic ulcer $n = 55$. 59 subjects in each treatment arm	59 patients treated with De Marco formula 0.15 mL/day intramuscular injection (DMF = combination of procaine HCl and polyvinylpyrrolidone), for 10 days, then twice weekly until wound healing or completion of a 6-week period. 59 patients treated with standard care	Infection outcomes: Amputation	Amputation rate 45.8% vs 25.4% (toes 30.4% vs 28.8%, transmetatarsal amputation 18.6% vs 8.5%) in the control group and DMF group, respectively (NS)	1+	Unknown risk of bias, unclear criteria for reason of amputation or level of amputation Little obvious evidence of benefit	Sponsored by Gen Cell
Hyperbaric oxygen therapy								
Doctor *et al*. [26]	RCT Single centre Open label Study quality, 3/9	30 patients with chronic diabetic foot ulcers, 15 subjects in both intervention and control group	All patients treated with systemic antibiotic therapy and wound debridement, 15 patients treated with HBOT, 15 treated conservatively 4 HBOT sessions of 45 min over 2 weeks. Antibiotic duration 3 days	Infection outcome: positive wound cultures Non-infection outcomes: hospital days, amputation and level	Hospital stay 41 vs 47 days, major amputation 2 vs 7, minor amputations 4 vs 2, pre-procedure positive wound culture 19 vs 16, post-procedure positive wound culture 3 vs 12, in the HBOT group versus the control group, respectively. All differences were not significant	1−	It was not described how many diabetic foot ulcers were infected, but most received antibiotics Method of randomization was not described Antibiotics used were based on sensitivity spectrum and included cephalosporins, aminoglycosides and metronidazole	No sponsor identified No evidence of benefit
Comparison of antibiotic regimens – skin and soft-tissue infection alone								
Bradsher and Snow [28]	RCT Multicentre Open label Study quality, 4/9	Subset of RCT in 84 patients with soft-tissue infection. Of these 84, 20 patients had DFI, 10 subjects in each treatment arm	10 patients with DFI treated with ceftriaxone, 10 with cefazolin Duration of antibiotic treatment unknown	Infection outcomes: only microbiological evaluation, elimination, reduction, persistence, relapse, reinfection	Elimination of infection: 6 vs 4, reduction: 3 vs 2, persistence: 1 vs 4 in ceftriaxone and cefazolin, respectively	1−	Insufficient data available for the DFI subgroup No clinical assessment in DFI subgroup	No sponsor identified
Lipsky *et al*. [34]	RCT Single centre Open label Study quality, 4/9	Outpatient infected diabetic foot ulcers $N = 56$, 27 vs 29	Oral clindamycin hydrochloride ($n = 27$) or cephalexin	Infection outcomes: Eradication of	No difference in eradication, clinical response or wound healing response between	1−	No ITT analysis No data on blinding of	Sponsored by the Department of Veterans

Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
		subjects in each treatment arm	($n = 29$) Duration of therapy 2 weeks. Additionally, 3 patients received an additional 2 weeks of antibiotic treatment after their initial course	bacteria by wound culture, clinical cure	the two antibiotics. Fifty-one infections (91%) were eradicated, 42 (75%) after 2 weeks of treatment; only 5 (9%) were initially treatment failures, and 3 (5%) were subsequently cured with further outpatient oral antibiotic treatment. After a mean follow-up of 15 months, no further treatment was required in 43 (84%) of the cured patients		patient/clinician/ assessor	Affairs and Upjohn Company Only study on clindamycin monotherapy First treatment trial of out-patients
Siami *et al*. [29]	RCT Multicentre Investigator blinded Study quality, 5/9	409 patients with skin and soft-tissue infection, of which 279 patients clinically evaluable, 54 patients with DFI, 25 subjects in each of the two treatment arms Patients with osteomyelitis were excluded	29 patients treated with clinafloxacin i.v., 25 with P/T i.v. with or without vancomycin (in case of MRSA). Duration of treatment for whole group (including group with DFIs): at least 3 days of i.v. therapy followed by oral therapy for a maximum total duration of 14 days. Median duration of treatment of patients that completed treatment was 13 days (total patients)	Infection outcomes: Clinical cure Microbiological eradication	15/29 clinically cured in clinafloxacin group vs 12/25 in pip/tazo group Microbiological eradication: 32/73 and 15/47 isolates eradicated for clinafloxacin and P/T groups, respectively	1+	Approximately one-third of patients not clinically or microbiologically evaluable	Sponsored by Parke-Davis Short duration of treatment, also relatively low rate of clinical cure
Clay *et al*. [14]	RCT Single centre Open label. (Veterans Admin.) Study quality, 3/9	DFU $N = 70$, only men with diabetes and lower extremity infection were included, 36 vs 34 subjects in each treatment arm	Group 1 $n = 36$ Metronidazole 1 g and 1 g ceftriaxone i.v. each day for a mean of 6.7 ± 3.3 days in patients with successful outcome 15 protocol violations Group 2 $n = 34$ Ticarcillin/clavulanate 3.1 g i.v. each 6 h for a mean of 6.1 ± 4.3 days in patients with	Temperature WCC Finger stick blood glucose Improvement of wound stage Creatinine clearance Costs	No statistically significant differences (NS) NS NS Stage changed 'minimally' – details not shown NS Cost saving of $61 per hospital admission in metronidazole/ceftriaxone group	1−	Men only 27 patients had antibiotics changed and no indication of whether the analysis was strictly per protocol No stated time of day for blood glucose measurement, and only undertaken in 39/70 Creatinine clearance assessed in only 31/70 'Treatment success' achieved in 29 patients	Sponsored by Roche Pharmacist-led study

DOI: 10.1002/dmrr

Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
			successful outcome 12 protocol violations				in Cef/Met and in 29 in the Tic/clav group (p = NS) Inappropriate measures of treatment success besides clinical staging (which is not standardized) Treatment duration is only assessed in those who achieved treatment success. This causes some doubt on the cost analysis No conclusions can be drawn from the study	
Lobmann *et al*. [27]	Cohort. Prospective Study quality, 4/8	180 diabetic patients with severe limb-threatening foot infection were consecutively enrolled. 300 patients were screened, 90 vs 90 subjects in each treatment arm	90 ceftriaxone vs 90 quinolones in addition to standard treatment of foot infection. Mean duration of treatment in ceftriaxone group 18.7 days, in quinolone group 23.8 days. Median duration of treatment in ceftriaxone group 11.5 days, and 16.5 days in the quinolone group	Non-infection outcomes Wound healing, amputation rate, length of stay Infectious: clinical (reaching Wagner I or 0) and microbiological cure rate of infection, duration of antibiotic therapy, need to change antibiotic therapy	Treatment with a third generation cephalosporin is as effective as a treatment with quinolones. Clinical response was achieved in 58.0% in the ceftriaxone group and in 51.1% in the quinolone group (NS). Fourteen days after initiation of treatment, the number of patients with microbiological isolates decreased in both groups (52 to 5 in the ceftriaxone group and 60 to 12 in the quinolone group). At hospital discharge, 66.0% of ceftriaxone and 64.4 of quinolone-treated diabetic ulcers were cured or improved. Median duration of antibiotic therapy 11.5 days for ceftriaxone vs 16.5 days for quinolone ($p < 0.01$). Need to change antibiotic therapy 7.8% ceftriaxone vs 16.7% for quinolones	2−	Clindamycin could be added in both groups (added in 27%) Not clear how many patients in each group received clindamycin. Definition of clinical response is unusual (change in Wagner grades)	Sponsored by Hoffmann La Roche
Harkless *et al*. [30]	RCT Multicentre Open label Study quality, 2/9	314 Patients with polymicrobial infections involving MRSA also	155 adult patients with moderate-to-severe infected diabetic foot	Clinical success (resolution of ulcer and of	Clinical efficacy rates (cure or improvement) were statistically equivalent overall	1−	Very large number of dropouts (38 and 44% non-evaluable)	Sponsored by Wyeth

Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
		received vancomycin 1 g q12h, *n* = 155 vs *n* = 159 subjects in each of two treatment arms	ulcers received P/T (4 g/0.5 g q8h), and 159 received A/S (2 g/1 g q6h) as a parenteral treatment Median duration of treatment 8.0 days P/T vs 8.5 days A/S	symptoms of infection, no addi-tional antibiotics needed) Bacteriological success (end of cure or end of treatment eradication or pre-sumed eradication)	(81% for P/T vs 83% for A/S), and median duration of treatment was similar in the clinically evaluable popula-tions (9 days for P/T, 10 days for A/S). Drug-related adverse events for both study drugs were comparable in frequency and type			
Lipsky and Stoutenburgh [31]	RCT Subset analysis of multicentre trial Investigator blinded Study quality, 4/9	*N* = 133, all subjects had a DFU with infec-tion, 47 vs 56 subjects in each of two treatment arms	Patients with a diabetic ulcer infection were prospectively stratified to ensure they were equally represented in the treatment groups, then randomized to either daptomycin (*n* = 47) [4 mg/kg every 24 h i.v.] or a pre-selected com-parator (*n* = 56) (vancomycin or a semi-synthetic penicillin) for 7–14 days Exact duration of treatment not given	Infection outcomes: Success rates microbiological adverse events	Of 133 subjects, 103 were clinically evaluable. Most infections were monomicrobial, and *Staphylococcus aureus* was the predominant pathogen. Success rates for patients treated with daptomycin or the comparators were not statistically different for clinical (66% vs 70%, respec-tively; 95% CI, −14.4, 21.8) or microbiological (overall or by pathogen) outcomes. Both treatments were gener-ally well tolerated, with most adverse events of mild to moderate severity	1−	Infection presumptively caused by Gram-positive organisms. 30 of 133 subjects were not clinically evaluable. 8 patients had MRSA infections: 1 in daptomycin group, 7 in vancomycin group Note: No ITT analysis	Sponsored by Cubist
Lipsky *et al*. [8]	2 RCTs consecutive, multicentre Double blind Study quality, 8/9	Mildly infected diabetic foot ulcers. *N* = 835 subjects, of whom 418 in the intervention group, and 417 in the control group	2 studies: 303 and 304: 418 subjects received the active topical agent pexiganan plus an oral placebo versus 417 subjects who received oral ofloxacin plus a topical placebo Mean duration 23 days in study 303 and 25 days in study 304. Median duration 27 days in	Infection outcomes: clinical cure or improvement of the infection, eradication of wound pathogens, bacterial resistance, adverse events Non-infection outcomes: wound healing	Although study 303 failed to demonstrate equivalence, study 304 and the combined data for the 2 trials demon-strated equivalent results (within the 95% confidence interval) for topical pexiganan and oral ofloxacin in clinical improvement rates (85–90%), overall microbiological eradication rates (42–47%) and wound healing rates. The incidence of	1++	Mild infection not adequately defined. Development of resistance in the oral antibiotic group Only study of oral versus topical treatment Low incidence of pexiganin resistance	Sponsored by Magainin and SKB

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Table (continued)

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			study 303 and 22 days in study 304		worsening cellulitis (2–4%) and amputation (2–3%) did not differ significantly between treatment arms. Bacterial resistance to ofloxacin emerged in some patients who received ofloxacin, but no significant resistance to pexiganan emerged among patients who received pexiganan. More adverse effects in the ofloxacin group			
Noel *et al*. [32]	RCT Multicentre Double blind Study quality, 6/9	Subgroup analysis of 257 people with DFI in a larger study of skin and skin-structure infections: total $N = 828$ (31% patients with DFI) 169 vs 89 subjects in each of the two treatment arms. Group allocation 2:1, only 222/257 were clinically evaluable	Group 1: 169 subjects: Ceftobiprole 500 mg i.v. 8 hourly Group 2: 89 subjects: Vancomycin 1 g each 12 h and ceftazidime 1 g each 8 h Both for 7–14 days. Mean duration of total population 9.0 days for ceftobiprole and 9.1 days for control group (per protocol analysis of $N = 828$)	Clinical outcomes assessed at TOC visit (7–14 days after EOT) and defined as: cure, failure and not evaluable Microbiological outcomes assessed at TOC visit (7–14 days after end of treatment): Eradication, presumed eradication, persistence, resumed persistence, colonization, superinfection, not evaluable	Clinically cured: Group 1 86.2% Group 2 81.8% (CI of comparison −5.4 to 15.7) No further details given for the DFI group	1+	No baseline details of the DFI patients Only outcome measure available for the DFI patients is the proportion of clinically cured in the clinically evaluable patients at TOC visit Efficacy of the two groups seemingly equivalent. Drug is currently not FDA or EMA approved. Centres targeted had high prevalence of MRSA	Sponsored by Johnson & Johnson
Vick-Fragoso *et al*. [33]	RCT Multinational Randomized open label Study quality, 4/9	Large multinational study of skin and soft-tissue infections, $N = 804$. Subset with DFI $n = 134$. Group 1, 63 subjects vs group	Group 1: sequential i.v./oral moxifloxacin 400 mg/day Group 2: sequential i.v./oral A/C 1000/200 mg three times daily Mean duration of antibiotic	Clinical success rate (success = total resolution or marked improvement of all	Group 1: 25/49 (51.0%) Group 2: 42/63 (66.7%) (5%CI for difference −34 to 2.7, formal statistical significance not calculated)	1−	No apparent difference in the subset with DFI No difference observed in the total population	Sponsored by Bayer

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Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
		2, 71 subjects. Total withdrawal 22/134	treatment 14.1 ± 5.5 days for moxifloxacin and 15.2 ± 5.4 days for A/C (i.v. and oral combined)	symptoms and signs; no additional or alternative antimicrobial treatment)				
Graham *et al.* [4], ertapenem versus P/T	RCT Multicentre Double blind Study quality, 5/9	540 adults with complicated skin and skin-structure infections. Of these, 98 had a lower extremity infection with diabetes, of which the data of 66 patients were evaluable Subjects with osteomyelitis were excluded	53 subjects received 1 g daily ertapenem with TID placebo infusions, compared with 45 subjects who received 3.375 g QID P/T Mean duration of therapy was 9.1 ± 3.1 days for ertapenem and 9.8 ± 3.3 days for P/T	Clinical cure	Clinical cure in evaluable patients (modified intention to treat analysis): Ertapenem group: 23/35 (66%) cure P/T group: 22/31 (71%) cure (no significant difference)	1–	Very limited demographical and baseline data on the subjects of the subgroup with diabetes Only data of 66 of 98 subjects were available for review and analysis More outcome measures are available for the total studied group but not for the subgroup of patients with diabetes-related lower extremity infection	Sponsored by Merck
Graham *et al.* [7], levofloxacin versus ticarcillin	RCT Multicentre Open label Study quality, 1/9	399 adults with complicated skin and skin-structure infections. Of these, 66 had an infected diabetic foot ulcer Subjects with osteomyelitis or who needed emergency surgery were excluded	Patients were randomized to 1 of the 2 study arms: Ticarcillin/clavulanate (3.1 g given i.v. every 4–6 h) with a switch to oral A/C (875 mg BID) at the investigator's discretion, or levofloxacin (750 mg given by mouth and/or i.v. QD). Subjects in both groups received 7–14 days of therapy. The randomization schedule was stratified by study centre and by diagnosis of diabetic ulcer Mean duration of therapy was 12.1 ± 4.9 days in the levofloxacin group and 12.1 ± 4.9 days in	Clinical cure	Clinical cure in evaluable patients in ticarcillin/clavulanate group 18/26 (69%) vs 16/28 (57%) in the levofloxacin group (no significant difference) Seven patients taking levofloxacin and 2 taking TC-AC had osteomyelitis diagnosed after admission to the study, resulting in 4 amputations Five of 9 of the osteomyelitis cases were due to diabetic ulcers	1–	Very limited demographical and baseline data on the subjects of the subgroup with diabetes Only data of 54 of 66 subjects were available for review and analysis More outcome measures are available for the total studied group but not for the subgroup of patients with diabetes-related lower extremity infection Not reported to which group the subjects with osteomyelitis were randomized	Sponsored by Johnson & Johnson Research and Development

Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
			the ticarcillin/ clavulanate group					
Comparison of antibiotic regimens – studies including patients with osteomyelitis								
Grayson *et al*. [39]	RCT Single centre Double blind Study quality, 9/9	Limb-threatening infection of the foot in 93 hospitalized subjects with 96 episodes of DFI, some despite previous antibiotic therapy. Prevalence of osteomyelitis 68% vs 56% episodes in the A/S and I/c groups, respectively. Group 1: 48 pisodes in 47 participants, group 2: 48 episodes in 46 participants One person was randomized in error	Group 1: A/S 2 g/1 g (A/S) i.v. 6-hourly Group 2: I/c 500 mg i.v. every 6 h Doses adjusted to renal function Mean duration of treatment in A/S group 13 ± 6.5 days vs 15 ± 8.6 days in the I/c group, follow-up period 1 year	Eradication of infection at 5 days Eradication of infection at EOT Microbiological eradication Failure at EOT Adverse reactions	Group 1 28/48 vs Group 2 29/48 Group 1 39/48 vs Group 2 41/48 ($p = 0.78$) Group 1 32/48 vs group 2 36/48 ($p = 0.5$) Group 1 8/48 vs Group 2 6/48 Group 1 16 vs Group 2 17	1++	High quality RCT No difference between two intravenous regimens in terms of resolution of signs of STI and of systemic signs There was a very high incidence of amputation 69 vs 58% for A/S and I/c, respectively Osteomyelitis – cannot be assessed in this way although did have follow-up for 1 year in this study, but they were also treated surgically	Sponsored by Pfizer High prevalence of osteomyelitis Osteomyelitis also treated with resection of bone 1 year follow-up No difference between narrow (gram-positive targeted) versus broad-spectrum antibiotics Research question must be to isolate osteomyelitis. But if included, need 1 year follow-up
Erstad and McIntyre [35]	RCT Single centre Double blind Study quality, 6/9	36 patients with DFI, majority superficial infection (56%). 18 patients in each of 2 treatment arms. 44% vs 28% suspected or proven osteomyelitis in the A/S group versus the cefotixin group, respectively	18 patients treated with A/S 3 g QID (A/S), 18 treated with cefoxitin, 2 g QID (Cef) for at least 5 days, in both groups combined with surgical intervention Mean duration of hospitalization 21.1 (range 6–58) days in A/S group, 12.1 (range 4–39) days in Cef group ($p = 0.06$)	Infection outcomes: Cure (=complete alleviation of signs or symptoms of infection), improvement, bacteriological response, amputation, duration of hospitalization	Cure 6% vs 39% ($p = 0.03$), improvement in 78% vs 50%, cure + improvement 15/17 vs 16/17, bacteriological response in 100% vs 73%, toe/ray amputation $n = 7$ vs $n = 7$, BKA $n = 1$ vs $n = 1$ and days of hospitalization 21.1 vs 12.1 in the A/S and cefotixin groups, respectively	1+	Unclear what day of treatment the assessment of clinical outcome was made	Sponsored by Pfizer Note: higher cure rate. Difficult to see why there is a difference in cure as opposed to cure plus improvement
Lipsky *et al*. [36]	RCT Multicentre Open label Study quality, 5/9	$N = 108$, 55 vs 53 subjects in the treatment arms. Prevalence of osteomyelitis 4/55	55 subjects i.v. then oral ofloxacin vs 53 subjects A/S, then oral A/C Mean duration of treatment	Infection outcomes Treatment of infection Cured or	No differences in outcomes between groups. Cured or improved 85% ofloxacin vs 83% A/S. The mean duration of therapy with the	1+	20 Subjects non-evaluable Persistence of streptococci in ofloxacin treatment group Infected bone was supposed to be	Sponsored by Johnson Pharmaceuticals

Table (continued)

Reference	Study design and score	Population	Intervention and control management	Outcomes	Differences and statistical results	Level of evidence (SIGN)	Comments	Opinion
		vs 1/53 in the ofloxacin and amoxicillin/sulbactam groups, respectively. Subjects with osteomyelitis included if the infected bone was removed	i.v. ofloxacin 7.8 days, oral 13.2 days, A/S i.v. 7.1, oral 12.0 days, duration of treatment in osteomyelitis: ofloxacin i.v. 9.2 days oral 11.5 days, A/S i.v. 7.0, days, 12.9 days oral A/C	improved, mean duration of therapy	ofloxacin regimen was 7.8 days (range, 1–25 days) intravenously and 13.2 days (range, 3–25 days) orally. The mean duration of therapy with the aminopenicillin regimen was 7.1 days (range, 1–20 days) intravenously and 12.0 days (range, 1–24 days) orally. Patients with osteomyelitis received a somewhat longer course of intravenous therapy (mean duration, 9.2 vs 7.0 days, respectively) but a slightly shorter course of oral therapy (mean duration, 11.5 vs 12.9 days, respectively) than did patients with only soft-tissue infections		removed, but in the results it turned out that it was only removed in 71% Numbers of osteomyelitis do not seem to match in the tables	
Lipsky *et al.* [37]	RTC Multicentre Open label Study quality, 4/9	371 enrolled, of whom 10 were not treated, 241 vs 120 in each treatment arm Prevalence of osteomyelitis 24% vs 17% in the linezolid and A/S group, respectively	241 linezolid, 120 A/S and A/C. Mean duration linezolid 17.2 ± 7.9 days, A/S 16.5 ± 7.9 days Duration of i.v. linezolid therapy 7.8 ± 5.5 days, oral linezolid therapy 15.9 ± 7.4 days, duration of A/S therapy 10.4 ± 5.7 days, oral A/C therapy 15.0 ± 7.8 days	Infection outcomes: clinical cure and safety data	Overall, the clinical cure rates were statistically equivalent (linezolid 81% vs A/S 71%). Subjects with linezolid had a higher cure rate for infected DFU (81% vs 68%; $p = 0.018$) and in cases without osteomyelitis (87% vs 72%; $p = 0.003$) Significantly more anaemia, thrombocytopenia and discontinuation of therapy in the linezolid group. Any event 26.6% vs 10.0% in the linezolid group versus the A/S group, respectively ($p < 0.01$)	1−	Investigators diagnosed osteomyelitis in 77 patients. The analysis of clinical outcome by pathogen is a modified intent-to-treat population which consisted of patients in the intent-to-treat population with a baseline pathogen and evaluable clinical response of success or failure The clinical cure rate is actually a per protocol analysis instead of an ITT analysis	Sponsored by Pfizer Only study to show higher incidence of AEs in one group
Lipsky *et al.* [13]	RCT Multicentre Double blind Study quality, 7/9	586 subjects with a DFI classified as moderate to severe and requiring intravenous antibiotics, 295 vs 291 subjects in each treatment arm. 12% of subjects had leg	Intravenous ertapenem (1 g daily; $n = 295$) or P/T (3.375 g every 6 h; $n = 291$) given for a minimum of 5 days, after which oral A/C (875/125 mg every 12 h) could be given for up to 23 days	Infection outcomes Clinical cure, bacteria eradication, safety data	Of the 576 treated subjects, 445 were available for assessment at the end of intravenous therapy. Both baseline characteristics and favourable clinical response rates were similar for the 226 who received ertapenem and the 219 who received P/T (94% vs 92%, respectively).	1+	Dropout rate 23% analysed by modified ITT 12% were leg ulcers. Data on site missing in $n = 174$. Proportion of cure for organisms resistant to ertapenem (pseudomonas and enterococci) was similar to success rates of P/	Sponsored by Merck Only 11 days treatment duration

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		ulcers. Prevalence of osteomyelitis 8% vs 6% in the ertapenem and P/T groups, respectively. Osteomyelitis was surgically removed <48 h	Mean duration of treatment 11.1 days for ertapenem and 11.3 days for P/T. Mean duration of oral follow-up therapy 9.7 days		Rates of favourable microbiological responses (eradication rates and clinical outcomes, by pathogen) and adverse events did not differ between groups. No differences in number of adverse events		T Number of patients who received additional antibiotics is not mentioned	
Lipsky *et al*. [38]	RCT, Sub-analysis of multicentre Double-blind, double dummy study Study quality, 8/9	617 Subjects, hospitalized for DFI, 78 patients with DFIs available for treatment efficacy. Prevalence of osteitis 11% vs 20% in moxifloxacin versus P/T group, respectively. Bone infection was surgically 'fully or partially resected'	Moxifloxacin (400 mg/day) or P/T (3.0/0.375 g every 6 h) for at least 3 days, followed by moxifloxacin (400 mg/day orally) or A/C (800 mg every 12 h orally) Duration of treatment: moxifloxacin i.v. 6.7 days, oral 7.4 days, A/C 6.3 days i.v., 7.9 days oral	Infection outcomes: clinical response of the infection at TOC, 10–42 days post-therapy, pathogen eradication, safety data	Among 617 patients enrolled in the original study, 78 with DFIs were evaluable for treatment efficacy. Clinical cure rates at TOC were similar for moxifloxacin and P/T/A/C (68% vs 61%) for patients with infection ($p = 0.54$). Overall pathogen eradication rates in the microbiologically valid population were 69% vs 66% for moxifloxacin and comparator, respectively ($p = 1.0$) No differences in safety outcomes	1++	Patients with osteomyelitis were excluded if the bone could not be fully or partially resected	Sponsored by Bayer Short duration of total treatment
Senneville *et al*. [9]	Cohort Multicentre Investigator blinded Study quality, 4/7	50 patients with diabetic foot osteomyelitis treated in different centres, of whom 16 (32%) had already been treated for osteomyelitis of the foot	Bone culture based antibiotic therapy Duration of treatment 11.0 ± 4.1 weeks for success group and 12.4 ± 4.2 week for failure group ($p = 0.19$). In the two groups combined: 11.5 ± 4.2 weeks	Infection outcomes: Failure 18 (36%), 32 remission (64%). 20 predictive criteria were evaluated	Positive association: bone culture based antibiotic therapy 4 (22.2%) in failure group, 18 (56.3%) in remission group ($p = 0.02$). Multivariate analysis OR 4.78, CI 1.02–22.7 ($p = 0.04$)	2+	9 patients lost to follow-up There was variability in practice and antibiotic therapy among centres	No sponsor identified
Saltoglu *et al*. [5]	RCT Single centre Open label Study quality, 5/9	In patients with diabetes and severe DFI and who were known to have organisms sensitive to study drugs. Total number randomized $N = 64$, but two withdrawn early	Group 1 i.v. P/T 4.5 g 8 hourly, group 2: i.v. l/c 0.5 g 6 hourly, with glycopeptide added if MRSA positive ($n = 3$), with excision of infected bone and with negative pressure therapy if necessary Intended	Clinical success rate (success = total resolution of all symptoms and signs, without amputation) Relapse within 2 months of hospital discharge	Group 1: 14 (46.7%) Group 2: 9 (28.1%) ($p = 0.13$) 0/14 vs 2/9 21 days vs 24 days Complete in 96% in both groups 18 total amputations vs 22 total ($p = 0.739$) 22.5% of the whole group had a BKA No difference between groups ($p = 0.55$)	1−	Total number recruited was 64 and yet analysis conducted on only 62: technically per protocol analysis Despite inclusion criteria, microbiological data available in only 'approximately 80%' 57% isolated organisms were Gram-negative, reflecting disease duration and	Not sponsored

Table
(continued)

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		and not included in analysis. Group 1 $n = 30$ (osteomyelitis 73%), group 2 $n = 32$ (osteomyelitis 81%) ($p = 0.05$)	duration of treatment: 14 days for soft-tissue infection; 28 days for soft tissue plus bone but only 5 days if all infected bone removed surgically	Treatment duration Microbiological response Total amputations Major amputations Adverse events			previous treatment Mean duration of infection was 30 days and 40.5 days in the two groups – and yet all had had no antibiotics for 48 h prior to inclusion – which is surprising in people with severe infection	

ABPI, ankle : brachial pressure index; A/C, amoxicillin/clavulanate; AE, adverse event; A/S, ampicillin/sulbactam; BID, twice daily; BKA, below knee amputation; DFI, diabetic foot infection; DFU, diabetic foot ulcer; DMF, De Marco formula; EMA, European Medicines Agency; EOT, end of therapy; FDA, US Food and Drug Administration; G-CSF, granulocyte-colony stimulating factor; HBOT, hyperbaric oxygen therapy; ITT, intention-to-treat; I/c, imipenem/cilastatin; i.v., intravenously; MRSA, methicillin-resistant Staphylococcus aureus; NS, not significant; P/T, piperacillin/tazobactam; QID, four times daily; QD, once daily; RCT, randomized controlled trial; s.c., subcutaneous; SKB, Smithkline Beecham; STI, soft tissue infection; T/C, ticarcillin/clavulanate; TID, three times daily; TOC, test-of-cure; WCC, white cell count.

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