

## **Interventions in the management of infection in the foot in diabetes: a systematic review**

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## Summary

The expert panel on diabetic foot infection (DFI) of the International Working Group on the Diabetic Foot conducted a systematic review seeking all published reports relating to any type of treatment for infection of the foot in persons with diabetes published as of 30 June 2014. This review, conducted with both PubMed and EMBASE, was used to update an earlier one undertaken on 30 June 2010 using the same search string. Eligible publications included those that had outcome measures reported for both treated and a control populations that were managed either at the same time, or as part of a before and after case design. We did not include studies that contained only information related to definition or diagnosis, but not treatment, of DFI. The current search identified just seven new papers meeting our criteria that were published since the 33 identified with the previous search, making a total of 40 papers from the world literature.

The identified papers included 37 randomised controlled trials (RCTs) and 3 cohort studies with concurrent controls, and included studies on the use of surgical procedures, topical antiseptics, negative pressure wound therapy and hyperbaric oxygen. Among the studies were 15 RCTs that compared outcomes of treatment with new antibiotic preparations compared with a conventional therapy in the management of skin and soft tissue infection. In addition, 10 RCTs and one cohort study compared different treatments for osteomyelitis in the diabetic foot. Results of comparisons of different antibiotic regimens generally demonstrated that newly introduced antibiotic regimens appeared to be as effective as conventional therapy (and also more cost-effective in one study), but one study failed to demonstrate non-inferiority of a new antibiotic compared to a standard agent.

Overall, the available literature was both limited in both the number of studies and the quality of their design. Thus, our systematic review revealed little evidence upon which to make recommendations for treatment of DFIs. There is a great need for further well-designed trials that will provide robust data upon which to make decisions about the most appropriate treatment of both skin and soft tissue infection (SSTI) and osteomyelitis in diabetic patients.

**Keywords:** diabetes mellitus, diabetic foot infection, osteomyelitis, antibiotics, surgery, systematic review

**Abbreviations:** DFI = Diabetic Foot Infections; SSTI = skin and soft tissue infection; RCT = randomised controlled trial, ITS = interrupted time series; CBA = controlled before-and-after; IWGDF = International Working Group on the Diabetic Foot; NICE = National Institute for Health and Clinical Excellence; SIGN = Scottish Intercollegiate Guidelines Network; G-CSF = granulocyte-colony stimulating factors; NPWT = negative pressure wound therapy; HBOT = Hyperbaric oxygen therapy;

## **Introduction**

Diabetic foot infections (DFIs) are associated with considerable morbidity, with worsening quality of life and a marked increase in the risk of lower extremity amputation (1). Because the outcome of these infections is likely to be improved by appropriate treatment, we have reviewed the available evidence to help establish evidence-based criteria for selecting treatment. To date, three systematic reviews of studies of treatment of DFIs have been published (2-5). One of these was restricted to studies of subjects with osteomyelitis affecting the foot in diabetes (2), while the other two included skin and soft tissue as well as osteomyelitis in the diabetic foot (3-5). Of the latter two reviews, one was conducted by the International Working Group on the Diabetic Foot (IWGDF) (3) and the other by the National Institute for Health and Clinical Excellence (NICE, United Kingdom) (4,5). Other groups have published guidelines on DFIs as well, but these were not based on a systematic review of literature (6-9). The present report updates and, by consolidating the results of previous and current literature searches, replaces the IWGDF systematic review of treatment of DFI conducted in 2011 and published in 2012 (3). The review focuses on studies of therapeutic interventions, not on definitions of infection or on methods for diagnosis – whether clinical, microbiological or by imaging.

## **Materials and Methods**

The methods used in this systematic review were identical to those used for our previous systematic review of this topic (3). The PubMed and Excerpta Medica (Embase) databases were searched using the string described in Appendix A that was designed to identify all prospective and retrospective studies, in any language, that evaluated interventions for the treatment of foot infections in people aged 18 years or older who had diabetes mellitus, and which were published before 30 June 2014. Eligible studies included randomised controlled

trials (RCTs), case-control studies, prospective and retrospective cohort studies, interrupted time series (ITS) or controlled before-and-after (CBA) design studies. Studies in which subjects with DFIs formed part of the total population were only included if the data for the subgroup with diabetes were separately described. Case series, uncontrolled case series and studies with non-concurrent controls were excluded, as were studies that were not related to treatment of DFIs.

One author assessed each study identified by the search string, based on the title and abstract, to see if it met the eligibility criteria. For potentially eligible publications, pairs of authors independently reviewed the full, published paper to assess whether or not it met the eligibility criteria. If the two reviewers disagreed they worked to reach consensus, with input from a third reviewer, if necessary. Using specially prepared forms, the groups of reviewers recorded: study design, characteristics of subject populations, details of interventions, study outcomes and the duration of follow-up. Investigators scored all studies for methodological quality using scoring lists developed by the Dutch Cochrane Centre (10). Quality items were rated as „done“, „not done“, or „not reported“, with only those rated as „done“ contributing to the methodological quality score. When scoring the study design, authors applied equal weighting to each validity criterion.

The methodological quality score was translated into a level of evidence using the Scottish Intercollegiate Guidelines Network (SIGN) instrument as either level 1 (randomised controlled trials) or level 2 (case-control, cohort, CBA or ITS studies) (11). Studies were also rated as follows: ++ (high quality with low risk of bias); + (well conducted with low risk of bias); or, – (low quality with higher risk of bias). Co-reviewers worked to reach agreement on the findings from the data extraction and the evaluation of methodological quality of each paper, and described each study on a narrative basis. Because of the heterogeneity of study designs, interventions, follow-up and outcomes, we made no attempt to pool the results of the included studies. The evidence tables were compiled following collective discussion (see Tables 1-9).

## **Results**

The literature search identified a total of 13,365 papers (6,292 from PubMed, 7,073 from Embase), of which 5,848 were published between July 2010 and July 2014. Figure 1

summarises the flow diagram of the review process of all papers published by June 2014. After review of all titles and abstracts, 567 papers were selected for full text review. Of these, only 35 met the eligibility criteria for inclusion. We added five additional studies identified by means other than the literature search (12-16), one of which was published between 2010 and 2014 (16).

### Types of studies

Of the included studies, 35 were RCT's and 5 were cohort studies. One paper was actually a description of two studies in one publication (17). With the exception of one Chinese study, all papers selected for data extraction were published in English. In some papers, patients with diabetes and a DFI formed a subgroup, for example from among patients with various skin and soft tissue infections. We excluded these studies if insufficient detail was provided specifically on the diabetic foot subpopulation. Fourteen studies reported on the use of antibiotics in skin and soft tissue infection. Eleven studies were in patients with DFIs including osteomyelitis, of which one study was on the use of bone biopsy, another was a substudy of patients with soft tissue infections exclusively, and two were on surgery in diabetic foot osteomyelitis. Three studies reported on treatment with topical antiseptic agents. Two additional randomised trials assessed the use of topical antibiotic therapy when used either alone or in combination with systemic antibiotic treatment for a skin and soft tissue infection. Four studies reported on the role of surgery in DFI. Two studies described the financial costs of different antibiotic regimens. For treatment of DFIs we found five studies on the value of granulocyte-colony stimulating factors (G-CSF), one on negative pressure wound therapy (NPWT), and one study to hyperbaric oxygen treatment,

### Interventions for treatment of DFIs, by selected topics

#### *Early surgery in the management of infection (Table 1)*

Our search identified two studies that attempted to assess the value of early surgery in treating DFIs (18,19), both of which were single-centre studies on the effect of early surgery versus antibiotics alone in deep DFIs with or without osteomyelitis. The reported results of both studies was a significant reduction in the early surgery group for major amputation: from 27 to 13% in one study (18), and 8 to 0% in the other (19). Both studies, however, were limited by a high risk of bias, especially including lack of randomisation of the subjects and lack of standardised treatment protocols for surgical (or medical) treatment. Studies designed to answer questions about the role of surgery typically pose particular difficulties, such as

selecting similar patients, standardising operative techniques and post-operative care. . Two recent studies on the effect of predominantly surgical compared with solely antibiotic therapy in diabetic foot osteomyelitis are described in the section on osteomyelitis below (20,21).

#### *Economic aspects of antibiotic choice (Table 2)*

We identified two studies that compared economic aspects of different antibiotic regimens in the treatment of soft tissue DFIs. In one, among subjects admitted to hospital (22) they reported a total potential cost saving of \$61 per subject treated with once-daily ceftriaxone and metronidazole compared with four times daily ticarcillin/clavulanate. In the second study (23), a subgroup analysis of a larger RCT (24), the authors performed a cost-minimisation assessment comparing treatment with ertapenem versus piperacillin/tazobactam. Because piperacillin/tazobactam requires more frequent dosing 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 about \$6.

#### *Topical negative pressure wound therapy (NPWT) (Table 3)*

In the single paper we identified that reported two separate studies involving the use of topical negative pressure wound therapy (NPWT) (16), the first of which included no infection-related outcomes. In the second study, after surgical debridement 130 individuals with diabetes and an open wound or surgical dehiscence following minor amputation were assigned to receive either NPWT or one of a variety of advanced dressings. While healing was the main outcome, the authors also reported an endpoint called “infection control,” determined by clinical evaluation (extent of granulation tissue, reduction in exudate and visual aspects of the wound). When necessary, wound biopsies were taken to assess “microbiological control,” but there were no details provided. An unknown number of subjects received antibiotic treatment of undisclosed type. The authors suggested that there was a more rapid control of infection (10 days in the NPWT group versus 19 days in the control group). Because of missing details we could not assess the validity of the reported findings or draw conclusions about the usefulness of the findings (16).

#### *Topical treatment with antiseptic agents (Table 4)*

We identified four studies that compared the results of treating DFI with topical superoxidised water versus either soap or povidone iodine (25-28). One of these was a small single centre RCT that found that compared to controls, the diabetic foot ulcers of those

treated with superoxidised water had less periwound erythema (a reduction of 81% versus 44%), less odour, and more granulation tissue (25). A second non-blinded study found that post-surgical subjects treated with topical povidone iodine were treated with antibiotics significantly longer compared with those treated with superoxidised water (15.8 days versus 10.1 days,  $p=0.016$ ) (27). Both studies included long-term outcomes of wound healing, but neither specifically addressed the potentially adverse effects of treatment with other topical disinfectants in the comparator groups (25,27). A third study with thirty subjects compared the results of a single application of a topical antiseptic, either iodophor or rivanol, with a control group (26). There was a significantly reduced growth of bacteria after 24 hours in the iodophor group compared with either the rivanol or control group, but the clinical usefulness of this study is limited by the short follow-up period and use of strictly microbiological (rather than clinical) outcome criteria. The fourth study was an unblinded pilot RCT comparing three treatment arms for 66 subjects with a mildly infected diabetic foot ulcer: topical superoxidised water alone; oral levofloxacin plus saline; and, topical superoxidised water plus oral levofloxacin (28). There were no significant differences in the rate of clinical success among subjects in the three groups and the small sample size was insufficient for a non-inferiority analysis. In general, drawing conclusions from these four studies of superoxidised water treatment is limited by their weak trial designs, incomplete reporting and possible sources of bias.

We identified two additional studies to topical treatment, but because these involved topical antibiotics, rather than antiseptics, we have described them in the section on skin and soft tissue infection below (17,29).

#### *Granulocyte-colony stimulating factor (G-CSF) (Table 5)*

We identified five single centre RCTs examining the value of adjunctive use of granulocyte-colony stimulating factor (G-CSF) in DFIs (13,30-33). Patients had only soft tissue infection in four of the five studies, and associated osteomyelitis in one (32). In two studies the design was double-blinded; in one case the assessor was blinded, and in the other the patient was blinded. Time to infection resolution was significantly shorter for subjects who received G-CSF in one study (30), but not in the others. This study (30) also reported a shorter duration of intravenous antibiotic use in G-CSF-treated patients, but this was not observed in another study (31). Hospital length of stay was shorter for the G-CSF group in two studies (13,30), but not in a third (31). The percentage of patients who underwent surgical intervention was not statistically different between the two groups in the three studies that examined it

(13,30,32), nor was the time to elimination of wound pathogens in two studies (30,32). The results of these five studies are somewhat inconsistent and provide no clear evidence on which patients with a DFI might benefit in some clinically important way from the use of G-CSF. A published meta-analysis of these five studies concluded that adding G-CSF did not significantly affect the likelihood of resolution of infection, healing of the wound, or the duration of systemic antibiotic therapy; it was, however, associated with a significantly reduced likelihood of lower extremity surgical interventions (including amputation) and a reduced duration of hospital stay (34).

*De Marco formula (a formulation of procaine and polyvinylpyrrolidone) (Table 6)*

One study assessed intramuscular injection in subjects with diabetes and a DFI. In one study, investigators injected 0.15 ml/day of procaine and polyvinylpyrrolidone for ten days in 118 patients with a DFI affecting an ischaemic limb (35). This observer blinded, single centre, RCT found no significant difference between groups. It is hard to draw any solid conclusions from the study, because it was severely limited by missing details. Although one other study of this intramuscular preparation was published, it contained no infection-related outcomes, and it therefore did not add to the conclusions of the other report (36).

*Hyperbaric oxygen therapy (HBOT) (Table 7)*

Although there have been several studies of the potential value of hyperbaric oxygen treatment for diabetic foot ulcer healing, we have identified only one that reported infection-related outcomes. In this small, low-scoring, single-centre, open label RCT of treatment of patients with a chronic diabetic foot lesion, 15 subjects were treated with HBOT and the 15 control subjects were not. At least some of the reported patients clearly had a DFI and all were treated with topical antiseptics and systemic antibiotics. Although the authors claimed their results demonstrated “better local control of infection” (apparently based on fewer positive wound cultures after treatment) in the HBOT group, the small size, poor quality and non-standardised methods used in the study do not clearly support a benefit for HBOT in DFI (37).

*Skin and soft tissue infection (SSTI) (Table 8)*

The published studies of antimicrobial therapy that we selected for review predominantly used agents that targeted gram-positive bacteria. However, the previously published IWGDF guideline on DFIs (38) drew attention to emerging evidence of the increased prevalence of

gram-negative organisms, especially *Pseudomonas aeruginosa*, as pathogens in DFI in warm climates and developing countries (39-41).

Our review identified two studies on treatment of DFI with topical antibiotic agents. In one, the authors compared the results of treatment with a topical application of the antimicrobial peptide pexiganan versus with an oral antibiotic (ofloxacin) (17). This report consisted of two nearly identical studies, in which a total of 418 subjects received pexiganan plus an oral placebo and 417 subjects received oral ofloxacin plus a topical placebo. The combined data for the two trials demonstrated equivalent results in rates of clinical improvement, microbiological eradication and wound healing. The incidence of adverse events was higher in the ofloxacin group. The authors concluded that pexiganan may be of value in the treatment of clinical infection, but emphasised that further studies were required.

The other RCT on topical antibiotic therapy assessed the value of adjunctive treatment with a gentamicin-collagen sponge on the infected wound to systemic antimicrobial therapy in 56 subjects with a moderate DFI (29). All participants received standard wound care and systemic antibiotic therapy, but only half were randomised to receive the sponge. Compared to the group who were not treated with the sponge, the clinical cure rate for subjects in the gentamicin-collagen sponge group was worse at treatment day 7 (the designated primary outcome), but significantly higher two weeks after discontinuing treatment. The study was marred by a modification of the selection criteria (to enhance enrolment), failure to reach the recruitment target, and a high withdrawal rate, making it difficult to interpret the reported findings.

The bulk of the available literature on treatment of DFI centres on studies comparing outcomes with different systemic antibiotic regimens. Most of these studies were industry-sponsored and designed to demonstrate non-inferiority between a new agent and an accepted regimen. We identified a total of 12 RCTs and one cohort study that compared new products in the management of SSTI of varying severity with other commonly used antibiotic regimens, including (in roughly historical order): ceftriaxone versus cefazolin (42); clindamycin versus cephalixin (43); clinafloxacin versus piperacillin/tazobactam (44) ertapenem versus piperacillin/tazobactam (15); levofloxacin versus ticarcillin/clavulanate (14); ceftriaxone plus metronidazole versus ticarcillin/clavulanate (22); ceftriaxone versus quinolones (45); piperacillin/tazobactam versus ampicillin/sulbactam (46); daptomycin

versus a semi-synthetic penicillin or vancomycin (47); ceftobiprole versus vancomycin plus ceftazidime (48); moxifloxacin versus amoxicillin/clavulanate (49); moxifloxacin versus piperacillin/tazobactam (50); and, tigecycline versus ertapenem with or without vancomycin (51).

In studies that provided details the mean duration of administration of the antibiotics in subjects with skin and soft-tissue infection ranged from 6 to 28 days. In the single study in which all subjects were treated on an outpatient basis with an oral antibiotic regimen, the mean duration of therapy was two weeks (43). Clinical cure rates in all studies (for patients without osteomyelitis) ranged from 48% (44) to 90% (17).

With notable exceptions especially in more recent years (50,51), many of the studies were weakened by aspects of trial design and reporting in relation to SSTI in the diabetic foot. One of the higher quality studies compared therapy with moxifloxacin versus piperacillin/tazobactam in 233 subjects with an acute (<21 days duration), mild to severe DFI who required hospitalisation and initial parenteral antibiotic treatment for at least 48 hours (50). The authors reported no significant differences between the two regimens in the rates of clinical cure of infection, lower extremity amputation, adverse events or bacteriological success. The second high quality study compared results of therapy with tigecycline and ertapenem (with or without the addition of vancomycin) in hospitalised subjects with an acute, mild to severe DFI (51). The primary study enrolled subjects who had only skin and soft tissue infection, but the authors included a planned substudy in subjects with osteomyelitis that we discuss below. In the primary study, among 944 subjects treated for 11 to 12 days, the tigecycline regimen did not meet the primary study endpoint of non-inferiority to the ertapenem ± vancomycin regimen, for either the clinically evaluable or the clinical modified intention-to-treat populations. The percentage of adverse events and study discontinuations related to adverse events were both significantly higher in the tigecycline treated group; these were primarily related to nausea, vomiting and insomnia. Our overall conclusion from the studies of antibiotic treatment of skin and soft tissue infection in the foot of individuals with diabetes is that the treatments compared were broadly equivalent (see Table 1). The one instance in which equivalence was not demonstrated was in the large, well-designed evaluation of tigecycline, which was shown to not be non-inferior to ertapenem ± vancomycin and to have significantly higher adverse events (51).

### *Osteomyelitis (Table 9)*

We identified eleven studies in patients with DFI complicated by osteomyelitis. One study was on the value of bone biopsy (52), and another was a substudy of patients with soft tissue infections (51). Other studies of treatment of diabetic foot osteomyelitis included an RCT comparing predominantly surgical versus antibiotic therapy (20) and a retrospective cohort study of subjects managed with antibiotics alone versus subjects treated with antibiotics and minor surgery (21). The RCT was a single-centre study of 52 subjects with osteomyelitis of the forefoot who were randomised to treatment with either systemic antibiotic therapy (until ulcer healing, but to a maximum of 90 days) or conservative surgery (defined as the removal of infected bone without amputation) combined with only 10 days of systemic antibiotic therapy (20). There were no statistically significant differences between the two treatment groups in healing, time to healing or in ulcer recurrence after 12 weeks of follow-up, and complication rates were also similar. Although well planned, the study was limited by difficulty in finding patients who met enrolment criteria and the fact that all enrolled subjects had infection of the forefoot. Nevertheless, the results suggested that the outcome was broadly similar in those who had predominantly surgical therapy compared with those who had exclusively antibiotic therapy. The cohort study was a retrospective review over two years of subjects hospitalised with predominantly forefoot diabetic foot osteomyelitis (21). Among the 37 evaluable subjects, 15 were managed with antibiotic therapy (without surgery) and 23 with concomitant minor amputation surgery (undertaken at the bedside) along with antibiotic therapy. There were no significant differences in time to wound healing, duration of antibiotic administration, duration of hospitalisation or rate of recurrence at one year. The subjects in the group who underwent concomitant surgery had significantly higher rates of foot ischaemia and more severe infections, making it difficult to draw conclusions from this small retrospective study.

Our review identified a single cohort study that addressed the question of using bone biopsy to help select a targeted antibiotic regimen for primarily non-surgical management of diabetic foot osteomyelitis (52). 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 the antibiotic choice was based on bone culture than in those in whom therapy based on wound swab culture (82% versus 50%, respectively [ $p=0.02$ ]). 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 underwent a bone culture.

We found a total of eight other RCTs that included subjects with a DFI with osteomyelitis—either exclusively or as part of a described subset (12,24,51,53-57). Seven of these RCTs compared the use of a beta-lactam/beta-lactamase inhibitor combination antibiotic against one of the following agents: imipenem/cilastatin (12,53); ceftazidime (54); ofloxacin (55); linezolid (56), ertapenem (24); or, moxifloxacin (57). Results of all these studies reported no significant differences in outcomes between the different antibiotic regimens. Two other studies did report differences in an outcome (51,54). The first of these was a substudy of 118 participants with osteomyelitis in the large RCT comparing the use of tigecycline with ertapenem ± vancomycin discussed above in the skin and soft tissue infection section (51). After a follow up of 25-27 weeks, the ertapenem ± vancomycin treated group had statistically non-significant higher cure rates. As in those with just skin and soft tissue infection in this study, there was a significantly higher rate of adverse events in the tigecycline treated group. The authors did not mention if infected bone was always surgically removed in the substudy. In the other study 36 subjects were treated with either ceftazidime or ampicillin/sulbactam (54). The outcome of treatment was “cure or improvement” in 15 of 17 of the ampicillin/sulbactam treated patients, and 16 of 17 of the ceftazidime treated patients. There was no difference in microbiological outcomes, days of hospitalisations, or number of amputations.

The number of subjects with osteomyelitis included was low (<10%) in two (24,55) but substantial in the remainder. Infected bone was removed prior to inclusion in all studies. The clinical cure rate, although variously defined, was exceptionally low in both subject groups in one study (54), but ranged from 61% (57) to 94% (52,53) in others. Mean duration of antibiotic treatment was surprisingly short, ranging from 6 days (54) to 42 days (51). The investigators of the two studies of predominantly surgery versus antibiotic therapy prescribed antibiotics for up to 90 days in the antibiotics group and 10 days for the surgery group in the RCT (20), and 45 days and 48 days in the cohort study (21), respectively. The quality of most, but not all (see Table 1), of these studies was generally good and each reported no significant difference in outcome between the treatment arms or between oral and parenteral route of administration.

## Discussion

This review includes all studies in any language published before June 2014 of treatments of DFI in which an intervention group was compared with a concurrent control group. We have divided the studies by individual topic, the largest of which are treatments for SSTI and for infection including osteomyelitis. To some extent the separation of these two groups is arguable, as different definitions were used, the percentage with osteomyelitis was sometimes small and infected bone was removed prior to inclusion in nearly all trials. This may explain the apparent resolution of a substantial number of included cases labelled as having osteomyelitis with only a short course of antibiotic therapy. Optimally, studies of the treatment of osteomyelitis should include measures of long term disease remission in addition to the short term measures of microbiological response and apparent clinical cure.

We identified 40 papers that met our inclusion criteria, only seven of which were published in the last four years, but the quality of trial design has been generally better in recent years. There remains, however, a clear need for more high quality studies to underpin clinical practice in the management of DFI. Data are now available to justify the addition of some newer antibiotic regimens to the armamentarium for treating DFI and diabetic foot osteomyelitis, and evidence continues to emerge to justify the non-surgical management of many cases of osteomyelitis, but progress in other treatment related areas is limited. Thus, the antibiotic choice for most DFIs remains largely a matter of expert opinion, as do the criteria used to determine route and duration of treatment for both osteomyelitis and infections of skin and soft tissue alone. There is similarly no strong evidence on whether or not it is beneficial to use various adjunctive therapies upon which to justify any major revision of IWGDF infection guidance papers.

**Conflicts of interest:**

BAL: Research funding from Innocoll; consulting for Innocoll, Merck, Pfizer, Dipexium, Cubist, Cerexa, KCI/Acelity;

LL: is on the speaker's bureau for Osiris, Integra, PamLabs, Smit&Nephew; consultant for KCI, PamLabs, Innovacyn; Stock ownership in Prizm Medical; received research grants from Osiris, MacroCure, ThermoTrek, Integra, GlaxoSmithKline, KCI, Cardinal, Dipexium.

ES: speaker and received congress support from Sanofi-Aventis and Novartis; consulting and received congress support from Pfizer; consultant for Cubist;

EJP, JAS, EJB, MD, JE, SK, SVA, VUR, and WJ: none declared.

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## Appendix A

### Search strings

Date databases accessed: July 26<sup>th</sup> 2014

Date range: until June 1<sup>st</sup> 2014

### Pubmed 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) OR (systematic [sb]))) 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 (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 cephalixin OR ceftriaxone OR ceftiprome OR ceftaroline 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 cotrimoxazole 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**

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 ceftaroline 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)

Accepted Article

Table 1: Evidence table – (Early) surgery

Tan 1996 (18)	Retrospective cohort Single centre Study quality 3/8	112 subjects hospitalised for treatment of a total of 164 diabetic foot infections. Of these, 76 had a deep infection, and 65 had osteomyelitis.	Comparison of 2 groups: 77 treated with antibiotics + surgery (of which 46 had debridement and 31 local amputation) vs 87 infections treated with antibiotics but without surgery in the first 3 days after admission. Duration of treatment with antibiotics unknown	Infection outcome: Above ankle amputation	Above ankle amputation rate (during the same or a subsequent hospitalisation) 13.0% in the early surgical intervention group vs 27.6% in the group without early surgery (p<0.01)	2-	No information regarding appropriateness (or other aspects) of antibiotic treatment. High risk of bias as there is no assessment of infection severity and a high chance of indication bias	No sponsor identified.  Available evidence cannot confirm the role of surgery, as opposed to timing of intervention
Faglia 2006 (19)	Retrospective cohort Single centre Study quality 5/8	106 subjects with diabetes and a deep foot space abscess	Comparison of 2 groups: Subjects that received immediate surgical debridement after outpatient admission (n=43) vs subjects transferred from another hospital	Drainage without amputation:  One or more ray amputations:  Transmetatarsal	Immediate surgery: 9 vs no early surgery: 4  Immediate surgery: 21 vs no early surgery: 21  Immediate	2-	Low quality study despite the 5/8 score; too many variables studied and large differences at baseline between the groups	No sponsor identified

Lázaro-Martínez 2014 (20)	See osteomyelitis section below	without surgical debridement after a mean delay of 6.2 ±7.5 days without debridement (n=63). Duration of treatment with antibiotics unknown	amputation: Chopart amputation: Major amputation:	surgery: 12 vs no early surgery: 10 Immediate surgery: 1 vs no early surgery: 23 Immediate surgery: 0 vs no early surgery: 5 $X^2$ 24.4, $p < 0.001$	Concluded that delay in drainage increases the incidence and proximal level of amputation, but interpretation of the retrospective data are subject to a high possibility of bias	
Ulçay 2014 (21)	See osteomyelitis section below					

Table 2: Evidence table - Health economics

Clay 2004 (22)	See section: Comparison of antibiotic regimens – skin and soft tissue infection alone							
Tice 2007 (23)	RCT, Subset analysis based on multicentre, double-blinded study.  Study quality 6/9	Included only the 99 subjects from a larger diabetic foot infection study who were hospitalised for their entire course of i.v. treatment and who were clinically evaluable at the 10-day follow-up assessment.	Substudy of SIDESTEP (24), cost-minimisation assessment of ertapenem (1 g once daily, n=56) vs piperacillin/tazobactam (PT, 3.375 g, four times daily, n=43)	Infection outcomes: Mean days of treatment:  Total i.v. drug doses:  Total antibiotic (i.v. and oral) dosages:  Mean drug	Ertapenem 7.6 vs PT 7.4 (p=0.8) days  Ertapenem 7.5 vs PT 25.5 (p<0.0001)  Ertapenem 8.6 vs PT 26.8 (p<0.0001)	1+	High drop-out rate. Length of stay was a proxy measure. The length of stay might have been prolonged due to the trial design. Cost-savings entirely related to fewer doses given for a once daily drug (ertapenem) compared to a four times daily drug	Sponsored by Merck



Table 3: Evidence table - Topical negative pressure therapy (NPWT)

Dalla Paola 2010 (16)	Open label RCT with independent randomisation The paper contains two studies. Mentioned in this table are results of "Study II". 6/9	People with diabetes complicated by infected post-surgical foot wounds, and amputation sites, University of Texas wound classification II-III A and B. Prepared for closure by primary or secondary intent, following treatment with systemic antibiotics	Comparison of two groups: Negative pressure wound therapy (NPWT) n=65 vs advanced wound dressing (n=65), such as alginate, hydrofibre, silver-dressing, or polyurethanes, depending on the amount of exudate and presence of infection	Mean time to wound closure Time to infection control Major amputation Hours of surgery time	NPWT: 65±16 days Control: 98±45 days p=0.005 NPWT: 10 days Control: 19 days p=0.05 NPWT 0/65 Control: 3/65 NPWT: 2.5 hours Control: 6 hours p=0.02	1- Many details of method, intervention or outcome are omitted or presented only in graphic form No details given of methods for defining infection and infection related outcomes The authors did not report which subjects received additional antibiotics or how often which type of wound dressing was applied	No funding source identified. No statement of potential conflicts of Interest. Impossible to draw conclusions due to omission of details
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Table 4: Evidence table - Topical treatment with antiseptic agents

Martinez-De Jesus 2007 (25)	RCT Single centre Subject blinded. Study quality 4/9	Type 2 diabetes and infected, deep diabetic foot ulcers	Comparison of two groups with topical treatment: n=21 neutral pH superoxidised aqueous solution vs n=16 disinfectant, such as soap or povidone iodine. Duration of antibiotic treatment > 10 days	Odour, periwound cellulitis and granulation tissue	Compared to control subjects, odour reduction was achieved in all superoxide subjects (100% versus 25%; p<0.01) and surrounding cellulitis diminished in 17 subjects (80.9% versus 43.7%; p<0.001	I-	Alternate subject group allocation, yet different numbers in each group. Non-standardized wound classification criteria	No sponsor identified
Chen 2008 (26)	RCT Single centre Subject-blinded. Study quality 6/9	30 subjects with diabetic foot ulcers	Comparison of three groups: 10 diabetic foot ulcers treated with iodophor, 10 with rivanol, and 10 controls. One single application of topical treatment after ulcer debridement	Infection outcomes: Bacteria number in wound	Number of colonies after 24 hours / number of colonies at t=0 by group: 0.961 (control), 0.918 (rivanol) and 0.986 (Significantly less growth of bacteria	I+	Use of systemic antibiotics not mentioned. Study only looked at bacterial growth after 5 minutes and 24 hours Unclear if ulcers were clinically uninfected	No sponsor identified

Piaggi 2010 (27)	RCT Single centre Open label. Study quality 6/9	40 subjects with diabetes with post-surgical wounds, who had surgery for a diabetic foot infection.	Comparison of two groups: Topical superoxidised water (Dermacyn) vs povidone iodine. 20 subjects in each group. All subjects had systemic antibiotic therapy and surgical debridement if needed. Limb ischemia was an exclusion criterion. Treatment with piperacillin/tazobactam and metronidazole with or without teicoplanin	Infection outcomes: Use of antibiotics.	after 24 hours in the iodophor group compared with the rivanol and control groups)	Duration of antibiotic use: 10.1 ± 6.1 weeks superoxidised water group vs 15.8 ± 7.8 weeks in povidone iodine group (p=0.016).  Healing rate at 6 months 90% in superoxidised water vs 55% in iodine group (p=0.002).  Healing time 10.5 ± 5.9 in superoxidised	1+	2 subjects 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	Article translated from Chinese.	Sponsored by Oculus Innovative Sciences
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Landsman 2011 (28)	Open-label, three arm, pilot RCT  Study quality 5/9	67 subjects with mild diabetic foot infection, University of Teas 1B	Comparison of three groups: A. Only topical superoxidised water (Microcyn), 30 mL daily, n=21 B. Levofloxacin 750 mg oral once daily, with local saline placebo, n=21 C. Superoxidised water locally plus levofloxacin orally 750 mg once daily, N=25 Treatment for 10 days in all groups	Clinical success (defined as cure or improvement), microbiological response and safety	water group vs 16.5 ±7.1 in iodine group (p=0.007)	No statistical differences between groups for rates of clinical success, although there was a trend towards more successful outcomes in the groups of subjects treated with superoxidised water. 75%, 52% and 72% in groups A, B and C, respectively)	1-	Results inconclusive because wound parameters vary. Results given for only 66 of 67 for ITT analysis. Study too small to show the implied non-inferiority. No detail on microbiological outcomes. 8 subjects lost to follow-up	Investigators are members of the „Oculus Collaborative Group“ and the study was funded by Oculus Innovative Sciences. No conflict of declared.
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Table 5: Evidence table - Granulocyte-colony stimulating factor (G-CSF)

Gough 1997 (30)	RCT Single centre Double blind Study quality 9/9	40 subjects with diabetes with moderate (PEDIS Grade 3) infection of DFU.	Comparison of two groups: G-CSF 5µg/kg adjusted on basis of WCC, for 7 days vs saline placebo. 20 subjects in both treatment arms. Both groups received the combination of i.v. ceftazidime, amoxicillin, flucloxacillin, and metronidazole, for a mean duration 8.5 days for subjects in the G-CSF group and 14.5 days for subjects in the control group (p= 0.02)	Infection outcome measures: 1. Time to resolution of infection: 2. Total time of intravenous antibiotics: 3. Hospital length of stay 4. Need for surgery 5. Time taken to eliminate pathogens from wound	G-CSF: 7 (5-20) days Placebo: 12 (5-93) days, p=0.03 G-CSF: 8.5 (5-30) days Placebo: 14.5 (8-63) days, p=0.02 G-CSF: 10.0 (7-31) days Placebo: 17.5 (9-100) days, p=0.02 G-CSF: 0 Placebo: 4/20 (20%), p=0.114 G-CSF: 4 (2-10) days Placebo: 8 (2-75) days, p=0.02	i ++	Well-designed RCT showing significant benefit in moderate infection. the results are reflected in the meta-analysis (34), which concluded that G-CSF did not have a significant benefit with regard to either resolution of infection or healing of wounds, although there was a significant reduction in the need for lower	Sponsored by Amgen
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Yönem, 2001 (31)	RCT, Single centre, Blinding unknown Study quality 2/9	30 subjects with cellulitis or Wagner grade $\leq 2$	Comparison of two groups: 15 subjects treated with standard treatment (parenteral antibiotics and wound care) vs 15 subjects treated with standard treatment + G-CSF 5 $\mu\text{g}/\text{kg}$ Duration of antibiotic treatment 22.9 $\pm$ 2.0 days in GCSF 22.3 $\pm$ 1.9 days in control group	Non-infection outcome: 6. Effect of GCSF on generation of neutrophil superoxide Infection outcomes: Time to resolution of infection, duration of hospitalisation, duration of parenteral antibiotic administration, need for surgical intervention	G-CSF: 16.1 (4.2-24.2) nmol per $10^6$ neutrophils/30 mins, Placebo 7.3 (2.1-11.5) $p < 0.0001$	1-	Also includes results of respiratory burst, granulocyte count etc. Typing error in abstract ( $p < 0.05$ should be $p > 0.05$ )	extremity surgery	No sponsor identified
De Lalla 2001 (32)	RCT, not placebo controlled, Single	Severe limb-threatening foot infection, all with	Comparison of two groups: Conventional treatment plus G-CSF 263 $\mu\text{g}$ sc daily for 21	1. Cure (complete closure of the ulcer without	At 3 weeks: G-CSF 0 vs controls 0 At 9 weeks:	1+	No effect of G-CSF on eradication of infection		No sponsor identified

Kästenbauer 2003 (33)	RCT Single centre Subject-	osteomyelitis and diabetes (N=40) Excluded subjects with ankle-brachial index <0.5 or ankle systolic pressure <50mmHg, and subjects with serum creatinine >1.6mg/100mL.	days vs conventional treatment (no placebo). 20 subjects in each treatment group Mean duration of antibiotics 68.9 ±29.2 days for G-CSF subjects and 58.7± 23.7 for controls (not significantly different). Antibiotic therapy consisted of ciprofloxacin 400 mg twice daily plus clindamycin 900 mg three times daily for severe infections and ciprofloxacin 750 mg orally twice daily and clindamycin 300 mg four times daily for less serious infections.	signs of bone infection) 2. Improvement of (eradication of pathogens in addition to marked or complete reduction of cellulitis but ulcer healing incomplete or persistent osteomyelitis 3. Failure (absence of any clinical improvement) or amputation for persistent infection	G-CSF 7 vs controls 7, p=1.0 At 3 weeks: G-CSF 12 vs controls 9, p=0.34 At 9 weeks: G-CSF 8 vs controls 4, p=0.17  At 3 weeks: G-CSF 8 vs controls 11, p=0.34 At 9 weeks: G-CSF 5 vs controls 9, p=0.19 Subjects who received G-CSF did not have an earlier resolution	Differences with other studies relating to prevalence of osteomyelitis and choice of outcome measures	Sponsored by Amgen  contrast with
			Comparison of two groups: subjects G- CSF group (n=20) initial daily dose of	Infection outcomes: Infection scores pre- vs post-	1+	Infection score non-validated	

<p>blinded Study quality 7/9</p>			<p>either 5 µg/kg G-CSF, vs placebo group (n=17) 0.9% sterile saline solution, s.c.. Subjects were treated with i.v. clindamycin and ciprofloxacin, followed by oral if necessary, 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</p>	<p>treatment, putrid smell, erythema, oedema</p>	<p>of clinically defined infection compared with placebo subjects</p>		<p>reference [21]</p>
<p>Viswanathan 2003 (13)</p>	<p>RCT Single centre Double blind</p>	<p>N=20, with extensive cellulitis, Wagner grade 2-3 ulcers</p>	<p>Comparison of two groups: daily dose of 5 µg/kg body weight G-CSF vs placebo (0.9% sterile saline solution),</p>	<p>Improvement of cellulitis: Surgery:</p>	<p>G-CSF: 9 Placebo 3 (N.S.) G-CSF: 0 Placebo 3 (N.S.)</p>	<p>Published as letter: many details are omitted. Uncertain if</p>	<p>Sponsored by Amgen</p>

	Study quality 3/9		<p>injected subcutaneously. 10 subjects in each treatment arm.</p> <p>Duration of treatment with G-CSF 10 days.</p> <p>Antibiotics in both groups were ofloxacin and metronidazole i.v. twice daily (unreported dosage)</p>	Hospital length of stay:	G-CSF 7.4 Placebo 8.8 ( $p=0.02$ )		outcome of hospital length of stay is actually time to resolution of cellulitis
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Table 6: Evidence table - Procaine hydrochloride plus polyvinylpyrrolidone (De Marco formula)

Duarte 2009 (35)	RCT, Single centre Assessor blinded, Study quality 7/9	118 subjects with ischaemic diabetic foot infection, of which Ischaemic gangrene n=63, ischemic ulcer n=55.	Comparison of two groups: 59 subjects treated with De Marco Formula (DMF) 0.15 ml/day intramuscular injection, for ten days, then twice weekly until wound healing or completion of a 6- week period vs 59 subjects treated with standard care. Standard care included use of penicillin, chloramphenicol, amikacin or ciprofloxacin, depending on the culture results.	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 (N.S.)	I +	Unknown risk of bias, unclear criteria for reason of amputation or level of amputation. Little obvious evidence of benefit. Authors do not mention further details of microbial data or details on antibiotic treatment.	Sponsored by Gen Cell
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Table 7: Evidence table - Hyperbaric oxygen therapy

Doctor 1992 (37)	RCT, Single centre Open label. Study quality 3/9	30 subjects with chronic diabetic foot ulcers.	Comparison of two groups: 15 subjects treated with hyperbaric oxygen treatment (HBOT) vs 15 treated without HBOT. All subjects treated with systemic antibiotic therapy and wound debridement, 4 HBOT sessions of 45 minutes over 2 weeks. Antibiotic treatment was with metronidazole, usually combined with ceftriaxone or aminoglycosides depending on the sensitivity patterns of the cultured bacteria for a duration of 3 days.	Infection outcome: positive wound cultures. Non-infection outcomes: hospital days, amputation rate 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 vs the control group, respectively. All differences were statistically non-significant	i - No description of how many diabetic foot ulcers were infected, but most received antibiotics. No description of method of randomisation.	No sponsor identified. No evidence of benefit
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Table 8: Evidence table - Comparison of antibiotic regimens – skin and soft tissue infection alone

Lipsky 2008 (17) (Topical antibiotic therapy)	2 RCTs consecutive, multicentre, double-blinded. Outpatient 2 studies: 303 and 304 Study quality 8/9	Mildly infected diabetic foot ulcers. N=835 subjects.	Comparison of two groups: 418 subjects received the active topical agent pexiganan plus an oral placebo vs 417 subjects that received oral ofloxacin 400 mg twice daily plus a topical placebo. Mean duration 23 days in study 303 and 25 days in study 304. Median duration 27 days in study 303 and 22 days in study 304	Infection outcomes: clinical cure or improvement of the infection, eradication of wound pathogens, development of 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 demonstrated 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 worsening	I++	Severity of infection not adequately defined (done before guideline definitions available). Development of resistance in the oral antibiotic group.  Only study of oral vs topical treatment; suggests topical therapy alone may be adequate (for appropriately selected subjects)  Low incidence of pexiganan resistance	Sponsored by Magainin and SmithKlineBeecham
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Lipsky 2012 (29)	Pilot open label (with exception)	Moderate diabetic foot infections, with	Comparison of two groups with a 2:1 randomisation:	Primary: clinical cure on Day 7	cellulitis (2%-4%) and amputation (2%-3%) did not differ significantly between treatment arms. Bacterial resistance to ofloxacin emerged in some subjects who received ofloxacin, but no significant resistance to pexiganan emerged among subjects who received pexiganan. More adverse effects in the ofloxacin group	1+	Some reported change in selection criteria suggests	Unbalanced emphasis on occasional
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<p>(Topical antibiotic therapy)</p>	<p>of microbiological results) multi-centre RCT to determine safety and potential benefit"</p>	<p>or without osteomyelitis (IDSA classification) N=56 Exclusion criteria: Systemic antibiotics in preceding two weeks; peripheral artery disease (Ankle brachial index &lt;0.7) or poor glycaemic control (HbA1c &gt;10%)</p>	<p>One group was treated with gentamicin collagen topical sponge 5x5 cm (50 mg of gentamicin sulphate equivalent to 32.5 mg gentamicin base) or 10 x10 cm (130 mg gentamicin base) depending on ulcer size, plus standard of care n=38 vs a control group which received standard of care (including 750mg levofloxacin once daily orally or intravenously or alternative, depending on sensitivities) N=18 Treated for at least 7 days, and up to 28 days</p>	<p>Clinical cure at test of cure visit (for evaluable subjects) Microbiological : eradication of baseline pathogens</p>	<p>p=0.017 Gentamicin sponge: 22/22 Control: 7/10 p= 0.024 Gentamicin sponge: 20/26 Control: 1/8 P&lt;0.001</p>	<p>initial slow recruitment. The study was also discontinued prior to achieving the intended sample size (N=75) for the same reason. Only 33 of 56 completed study. 20 apparently recruited in error ("ineligibility")</p>	<p>statistical differences between groups in some measures at selected times give the appearance of benefit in the intervention group. „Test of cure“ data are a per protocol rather than intention to treat analysis. All investigators were funded by Innocoll,</p>
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Bradsher 1984 (42)	RCT, Multicentre Open label, Study quality 4/9	Subset of RCT in 84 subjects with soft tissue infection. Of these 84, 20 subjects had diabetic foot infection.	Comparison of two groups: 10 subjects treated with ceftriaxone 1 g once daily i.m. or i.v., vs 10 subjects treated with cefazolin 1 g three to four times daily i.v.. Duration of antibiotic treatment not stated	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 treated subjects, respectively.	1-	Insufficient data available for the diabetic foot infection subgroup. No clinical assessment in diabetic foot infection subgroup	the manufacturer Small study No sponsor identified
Lipsky 1990 (43)	RCT, Single centre Open label Study quality 4/9	Outpatient infected diabetic foot ulcers N=56.	Comparison of two groups: 27 subjects received oral clindamycin hydrochloride 300 mg four times daily vs 29 who received cephalixin 500 mg four times daily. Duration of therapy 2 weeks. Additionally, 3	Infection outcomes: Eradication of bacteria by wound culture, clinical cure	No difference in eradication, clinical response or wound healing response between the two antibiotic groups. 51 infections (91%) were eradicated, 42 (75%) after 2 weeks of	1-	No ITT analysis. No data on blinding of subject/clinician/assessor	Sponsored by the Department of Veterans Affairs and Upjohn Company. Only study on clindamycin

Siami 2001 (44)	RCT, multicentre Investigator blinded, Study quality 5/9	409 subjects with skin and soft tissue infection, of which 279 subjects clinically evaluable; of these 54 subjects with diabetic foot infection.	Comparison of two groups: 29 subjects treated with clinafloxacin iv 200 mg twice daily followed by clinafloxacin 200 mg twice daily orally vs 25 subjects treated with	Infection outcomes: Clinical cure  Microbiological eradication	15/29 clinically cured in clinafloxacin group vs 12/25 in PT/AC group.  Microbiological eradication: clinafloxacin 32/73 vs PT/AC	1+	Approximately one third of subjects not clinically or microbiologically evaluable	Sponsored by Parke-Davis.  Short duration of treatment; relatively low rate of clinical cure
			subjects received 2 more weeks of antibiotic treatment after their initial course		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 subjects			monotherapy  First treatment trial of outpatients treated orally

Graham	RCT	Subjects with osteomyelitis were excluded.	<p>piperacillin/tazobactam iv 3,375 mg four times daily (PT) (with vancomycin in the PT group in case of cultured or suspected enterococci or MRSA), followed by oral amoxicillin/clavulanate 500/125 mg (AC) three times daily .</p> <p>Duration of treatment for whole group (including group with DFIs): at least 3 days of iv therapy followed by oral therapy for a maximum total duration of 14 days. Median duration of treatment for subjects who completed treatment was 13 days (total subjects)</p>	Clinical cure	Clinical cure in 1-	Very limited	Sponsored
		15/47 isolates eradicated					

2002 (15)	Multicentre Double blind Study quality 5/9	complicated skin and skin-structure infections. Of these, 98 had a lower extremity infection with diabetes, of which the data on 66 subjects were evaluable. Subjects with osteomyelitis were excluded	groups: 53 subjects received ertapenem iv 1 g daily with three times daily placebo infusions vs 45 subjects who received piperacillin/tazobactam iv (PT) 3.375 g four times daily  Mean duration of therapy was 9.1±3.1 days for ertapenem and 9.8±3.3 days for PT	evaluable subjects (modified intention to treat analysis): Ertapenem group: 23/35 (66%) cure, PT group: 22/31 (71%) cure (no significant difference)	demographical and baseline data on the subjects of the subgroup with diabetes. Only data for 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 subjects with diabetes related lower extremity infection	by Merck
Graham 2002 (14)	RCT Multicentre Open label Study	399 adults with complicated skin and skin-structure infections. Of these, 67 had an	Comparison of two groups: 31 subjects received ticarcillin/clavulanate (TC, 3.1 g given iv four to six times	Clinical cure in evaluable subjects in TC/AC group 18/26 (69%) versus 16/28 (57%) in the levo	Very limited demographical and baseline data on the subjects of the subgroup with diabetes	Sponsored by Johnson & Johnson Research and Development

Clay 2004	RCT	70 men with infected diabetic foot ulcer. Subjects with osteomyelitis or who needed emergency surgery were excluded	quality 1/9	<p>daily), with a switch to oral amoxicillin/clavulanate (AC, 875 mg twice daily) at the investigator's discretion, vs 36 subjects who received levofloxacin (levo, 750 mg daily, orally or iv). Subjects in both groups received 7-14 days of therapy. The randomization schedule was stratified by study centre and by diagnosis of diabetic ulcer.</p> <p>Mean duration of therapy was 12.1±4.9 days in the TC/AC group and 12.1±4.9 days in the levo group and</p> <p>Comparison of two</p>	Temperature:	No statistically	1-	<p>group (no significant difference) Seven subjects taking levo and 2 taking TC/AC had osteomyelitis diagnosed after admission to the study, resulting in 4 amputations. Five of nine of the osteomyelitis cases were due to diabetic ulcers</p>	<p>Only data of 54 of 66 subjects were available for review and analysis. More outcome measures are available for the total studied group than for the subgroup of subjects with diabetes related lower extremity infection. Not reported to which group the subjects with osteomyelitis were randomised</p>	Only men	Sponsored
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(22)	Single centre Open label	infected diabetic foot ulcers	groups: 36 subjects received 1g ceftriaxone 1 g IV + metronidazole 1 g (Cef/MTZ) once daily vs 34 subjects who received ticarcillin/clavulanate 3.1 g IV (TC) four times daily  In the Cef/MTZ group, subjects were treated for a mean of 6.7 ± 3.3 days in subjects with successful outcome. 15 protocol violations were observed.  In the TC group, subjects were treated for a mean of 6.1 ± 4.3 days in subjects with successful outcome. 12 protocol violations	WBC count:  Finger stick blood glucose:  Improvement of wound stage:  Creatinine clearance:  Costs:	significant differences (NS)  NS  NS  Stage changed “minimally” – details not shown  NS  Cost saving of \$61 per hospital admission in cef/MTZ group	included. 27 subjects had antibiotics changed and no indication of whether the analysis was strictly <i>per protocol</i> . 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 subjects in Cef/MTZ and in 29 in the TC group (p=NS)  Non-validated measures of	by Roche Pharmacist-led study
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Lobmann 2004 (45)	Prospective cohort study.  Study quality 4/8	180 subjects with diabetes enrolled (as matched pairs) with severe, limb-threatening foot infection from among 300 consecutively enrolled subjects.	Comparison of two groups: 90 subjects were treated with ceftriaxone 2 g daily i.v. vs 90 subjects treated with quinolones (ofloxacin (n=8), ciprofloxacin (n=58), levofloxacin (n=24), IV or oral) in addition to standard	Non-infection outcomes: wound healing, amputation rate, length of stay Infectious outcomes: clinical (reaching Wagner grade 1 or 0) and microbiological	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	Clindamycin added in 27% of subjects (total). Not clear how many subjects in each group received clindamycin. Definition of clinical response is unusual (change in Wagner grades)	treatment success besides clinical staging (which is not standardized). Treatment duration is only assessed in those who achieved treatment success, casting doubt on the cost analysis No conclusions can be drawn from the study	Sponsored by Hoffmann La Roche
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			<p>treatment of foot infection. In both groups, the combination with clindamycin was allowed.</p>	<p>cure rate of infection, duration of antibiotic therapy,</p>	<p>group (NS), 14 days after initiation of treatment the number of subjects 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 (mean 18.7) days for</p>		
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Harkless 2005 (46)	RCT Multicentre Open label Study quality 2/9	314 subjects with moderate to severe polymicrobial diabetic foot infections; subjects with infections involving methicillin-resistant <i>Staphylococcus aureus</i> also received vancomycin 1 g q12h.	Comparison of two groups: 155 subjects received PT (4 g/0.5 g iv three times daily) vs 159 subjects who received AS (2 g/1 g four times daily iv)	Clinical success: (ulcer healing and of symptoms and signs of infection, no additional antibiotics needed) Bacteriological success: end of cure or end of treatment eradication or presumed eradication of causative pathogens	ceftriaxone vs 16.5 (mean 23.8) days for quinolone (p<0.01). Clinical efficacy rates (cure or improvement) were statistically equivalent overall (81% for PT vs. 83% for AS), and median duration of treatment was similar in the clinically evaluable populations (nine days for PT, 10 days for AS). Median duration of treatment was 8.0 days in the PT vs 8.5 days in the AS group. Drug-related adverse	1-	Very large number of dropouts (38% and 44% non evaluable)	Sponsored by Wyeth Weak design makes it difficult to draw conclusions.
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Lipsky 2005 (47)	RCT Subset analysis of multicentre trial Investigator blinded, Study quality 4/9	133 subjects with an infected diabetic foot ulcer with infection.	Subject were prospectively stratified to ensure they were equally represented in the treatment groups, then randomised to either daptomycin (n=47, 4 mg/kg every 24 h i.v.) or a pre-selected comparator (vancomycin 1 g twice daily or a semi-synthetic penicillin 4-12 g daily) (n=56) for 7-14 days. Exact duration of treatment not given	Infection outcomes: Clinical (cure, improvement, failure) and microbiological success rates. Adverse events	Of 133 subjects, 103 were clinically evaluable. Most infections were monomicrobial, and <i>Staphylococcus aureus</i> was the predominant pathogen. Success rates for subjects treated with daptomycin versus the comparators were not statistically different for clinical (66% versus 70%, respectively; 95%	events for were comparable in frequency and type for the two groups	1-	Infection presumptively caused by gram-positive organisms. 30 of 133 subjects were not clinically evaluable. 8 subjects had MRSA infections: 1 in daptomycin group, 7 in vancomycin group. Note: No ITT analysis	Sponsored by Cubist
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Noel 2008 (48)	RCT Multicentre Double blind Study quality 6/9	Subgroup analysis of 257 people with DFI in a larger study of 828 subjects with skin and skin structure infections: (31% of subjects with DFI)	Comparison of two groups: 169 subjects received ceftibiprole 500mg IV every 8 hours, vs 89 subjects received vancomycin (vanco) 1g every 12 hours with ceftazidime (cefta) 1g every 8 hours (group allocation 2:1)  Both groups received therapy for 7-14 days.	Clinical outcomes assessed at test of cure visit (7-14 days after end of therapy) and defined as: cure, failure, or not evaluable  Microbiological outcomes assessed at test-of-cure visit and defined as:	CI, -14.4, 21.8) or microbiological (overall or by pathogen) outcomes. Both treatments were generally well tolerated, with most adverse events of mild to moderate severity	1+	No baseline details of the DFI subjects. Only 222/257 subjects were clinically evaluable.  Only outcome measure available for the DFI subjects is the proportion of clinically cured in the clinically evaluable subjects at TOC visit.	Sponsored by Johnson & Johnson
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Vick-Fragoso (2009) (49)	RCT Multinational Randomised Open label Study quality 4/9	Study of 804 subjects with skin and soft tissue infections, Subset with diabetic foot infection: n=134. subject	Mean duration for total population 9.0 days for ceftibiprole and 9.1 days for vanco/ceftia group (per protocol analysis of N=828)	eradication, presumed eradication, persistence, resumed persistence, colonisation, superinfection, or not evaluable	Moxi: 25/49 (51.0%) AC: 42/63 (66.7%) (95% confidence intervals for difference -34 to 2.7, formal statistical significance not calculated)	1-	Efficacy of the two groups seemingly equivalent. Cefibiprole is available in some countries but currently not FDA or EMA approved. Centres participating in the study had a high prevalence of MRSA.	Sponsored by Bayer
		Comparison of two groups: 63 subjects received sequential IV/oral moxifloxacin (moxi) 400mg/day vs 71 subjects received sequential IV/oral amoxicillin/clavulanate (AC) 1000/200mg three times daily. Mean duration of	Clinical success rate (defined as total resolution or marked improvement of all symptoms and signs and no additional or alternative antimicrobial treatment)				No apparent difference in the subset with diabetic foot infection vs all soft tissue infections. No differences in outcomes observed in the total population. Total subjects withdrawn 22/134	

Schaper 2013 (50)	Double-blind, double dummy, multicentre  Study quality 9/9	Diabetes with soft tissue foot infection  IDSA infection severity: Mild 22 Moderate 168 Severe 11  233 randomised 27 lost to follow up	antibiotic treatment 14.1 ± 5.5 days for moxifloxacin and 15.2±5.4 days for amoxicillin/clav (i.v. and oral combined)	Comparison of two groups: 110 subjects received IV/Oral moxifloxacin (moxi, 400 mg/day) vs 96 subjects who received IV piperacillin/tazobactam (PT, 4000/500 mg, three times daily) followed by oral amoxicillin/clavulanate (AC, 875/125 mg, twice daily). Treatment duration 7-21 days (n=96)	Clinical cure  Incidence of amputation  Any secondary surgery  Adverse events  Death  Bacteriological success	Moxi: 69.9% PT/AC: 69.1%  Moxi: 8.2% PT/AC: 16.7%  Moxi: 20.9% PT/AC: 25.0%  Moxi: 30.9% PT/AC: 31.8%  Moxi: 3 PT/AC: 1  Moxi: 71.7% PT/AC: 71.8%  No significant differences	I++	Low percentage of male subjects compared with published literature  Enrolled subjects were required to have involvement of deep soft tissue (e.g., fascia, muscle layer) and the need for significant surgical intervention. Thus, unlikely that subjects with “mild” infections were actually included.	Well-designed and conducted study showing no significant differences between groups in clinical outcomes and adverse events  Study was designed, funded and analysed by manufacturer Bayer
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Lauf 2014 (51) Substudy also mentioned in the section on osteomyelitis below	Double-blind, phase III, multicentre RCT  Study quality 9/9	Diabetic foot infection with soft tissue involvement (primary study) N=955 randomised 944 modified intention to treat (mITT) group (813 clinically evaluable) 85% with T2DM 6 lost to follow-up  Substudy of subjects with osteomyelitis N=118 randomised 117 mITT	Comparison of two groups in both the primary study and the substudy  Primary study: 483 subjects received tigecycline 150mg once daily iv vs 472 subjects received ertapenem 1 g iv ± vancomycin (dosage not stated) iv  Substudy in osteomyelitis: Tigecycline group n=77 Ertapenem ± vancomycin n=41  Median duration of treatment Intervention: 11 days Control: 12 days	Primary study Clinical response mITT   Clinically evaluable (CE)  Adverse effects  Substudy Clinical response mITT	Tigecycline: 71.4% (n=477) Ertapenem: 77.9% (n=467) (adjusted analysis for non inferiority p=0.129) Tigecycline: 77.5% (n=408) Ertapenem: 82.5% (n=405)(adjusted analysis for non inferiority p=0.055)  Tigecycline: 71.1% Ertapenem: 57% p<0.001  Tigecycline: 35.8% (n=76) Ertapenem: 63.6% (n=41)	1++	Significantly higher rate of discontinuation because of adverse events in intervention group  No information on rates of surgery including amputation	Healthcare. Large well-designed and conducted trial that concluded that the tigecycline therapy did not meet the criteria of non-inferiority. In fact the study showed that tigecycline was clinically inferior to ertapenem in several analyses and associated with significantly more adverse
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Table 9: Evidence table - Comparison of antibiotic regimens – studies including subjects with osteomyelitis

Lázaro-Martínez 2014  (also mentioned in surgery section above) (20)	RCT Single centre  Study quality 4/9	52 subjects with diabetes complicated by osteomyelitis (all of the forefoot)	Comparison of two groups: 24 Subjects treated with systemic antibiotics until healing or for 90 days (no bone surgery) vs 22 subjects treated with conservative surgery (removal of infected bone without amputation)	Healing within 90 days  Median time to healing  Additional surgery  Death  Healed at 12 weeks  New ulcer at 12 weeks	No surgery: 18/24 Surgery: 19/22  No surgery: 7 weeks Surgery: 6 weeks  No surgery: 4 (1 minor amp) Surgery: 3 minor amp  No surgery: 2 Surgery: 0  No surgery: 19 Surgery: 15  No surgery: 2 Surgery: 4	1+	Highly selected population (only 52 Of 156 screened were enrolled)  Per protocol analysis with analysis of only 46 of 52 enrolled subjects.  Significant differences between groups at baseline in age, gender, coronary artery disease, antiplatelet treatment, BMI and retinopathy	Difficult to plan and conduct an RCT of surgery versus non-surgery and the formal scoring – with its lack of blinding – does not reflect this  The median duration of antibiotic use was not reported in each group but is presumed to be No surgery:
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Ulcaay 2014 (also mentioned in surgery section above) (21)	Retrospective study Study quality 3/8	37 subjects with diabetes hospitalised with osteomyelitis (forefoot 34; mid-/hind-foot 3)	amoxicillin/clavulanate 875/125 mg twice daily, or trimethoprim 160 mg/sulfamethoxazole 800 mg twice daily. The antibiotic regimen was modified according to the results of an antibiogram.	Time to healing  Total duration of antibiotics  Total days in hospital	No surgery: 265.2 ± 132.7 days Surgery: 222.6 ± 85.9 days  No surgery: 45.0 ± 21.7 days Surgery: 47.7 ± 19 days  No surgery: 37.2 ± 16.2 Surgery: 52.8 ± 40.2	2+	Significant differences between groups at baseline with more severe disease in the surgery group.  Indications for surgery not given.  Used antibiotic regimen not stated. Also, no information on resistance	7 weeks Surgery: 10 days	Difficult to draw conclusions because the groups are not comparable
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Senneville 2008 (52)	Retrospective cohort Multicentre Investigator-blinded. Study quality 4/7	50 subjects with diabetic foot osteomyelitis treated in different centres, of whom 16 (32%) had already been treated for foot osteomyelitis	Study seeking to identify criteria predictive of remission in nonsurgically treated subjects with diabetic foot osteomyelitis. Mean duration of treatment 11.0 ± 4.1 weeks for successfully treated group and 12.4 ± 4.2 week for failure group (p=0.19). Mean treatment duration in	Infection outcomes: Failure 18 (36%), 32 remission (64%). 20 predictive criteria were evaluated	Positive association with treatment success: Antibiotic therapy based on bone culture 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 subjects lost to follow up. There was variability in practice and antibiotic therapy among centres, specifically with more use of rifampin in subjects who had a bone-culture	prevalence stated. Given the origin of the paper (Turkey), the number of multiresistant pathogens was likely to be relatively large.  Reason for dropouts not stated.	No sponsor identified
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Grayson 1994 (53)	RCT Single centre Double blind  Study quality 9/9	Limb-threatening infection of the foot in 93 hospitalised subjects with 96 episodes of DFI, Prevalence of osteomyelitis 68% of episodes in the ampicillin/sulbac tam (AS) and 56% of episodes in the imipenem/cilasta tin (IC) groups,	the two groups combined: $11.5 \pm 4.2$ weeks. Antibiotics used not stated (except that more rifampin was used in certain participating centres)	Comparison of two groups: AS 2g/1g IV every 6 hours (48 episodes of infection in 47 subjects) vs IC 500mg IV every 6 hours (48 episodes of infection in 46 subjects) Doses adjusted to renal function. Mean duration of treatment in AS group $13 \pm 6.5$ days, vs 15 $\pm 8.6$ days in the IC group Follow-up period 1 year	Eradication of infection at 5 days:  Eradication of infection at End of Therapy (EOT): Microbiological eradication:  Failure at EOT:  Adverse reactions:	AS 28/48 vs IC 29/48  AS 39/48 vs IC 41/48 (p=0.78)  AS 32/48 vs IC 36/48 (p=0.5)  AS 8/48 vs IC 6/48  AS 16 vs IC 17	1++	High quality RCT  No difference between these two intravenous regimens in resolution of signs and symptoms of soft tissue infection and of systemic signs of infection. There was a very high incidence of amputation 69% for AS and 58% for IC, respectively	Sponsored by Pfizer  High prevalence of osteomyelitis , which was treated with resection of bone. 1 year follow-up  No difference between a relatively narrow
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Erstad 1997 (54)	RCT, Single centre Double blind  Study quality 6/9	36 subjects with diabetic foot infection, 56% of which were superficial. Suspected or proven osteomyelitis in 44% of ampicillin/sulbac tam (AS) group vs 28% of the cefoxitin (Cef) group.	Comparison of two groups: 18 subjects treated with AS 3 g IV every 6 hours vs 18 treated with Cef, 2 g IV every 6 hours for at least 5 days; in both groups combined with surgical intervention as needed.	Infection outcomes: Clinical cure (complete alleviation of signs or symptoms of infection) or improvement; bacteriological response; amputation rate; duration of hospitalisation	Clinical response: Cure in AS 6% vs Cef 39% ( $p=0.03$ ), improvement in AS 78% vs Cef 50%, cure + improvement in AS 15/17 vs Cef 16/17, Bacteriological response: In AS 100% vs in Cef 73%	1 +	Unclear what day of treatment the assessment of clinical outcome was made.  Higher cure rate in Cef group, but no difference between groups in cure + improvement in AS vs Cef group. Difficult to see why there is a	versus a broad spectrum antibiotic  Data on the specific outcomes of subjects with osteomyelitis could not be identified.  Sponsored by Pfizer
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Lipsky 1997 (55)	RCT Multicentre Open label Study quality 5/9	108 subjects with osteomyelitis included if the infected bone was removed. Prevalence of osteomyelitis 4/55 in ofloxacin (oflox) group vs 1/53 in the ampicillin/sulbactam followed by amoxicillin/clavulanate (AS/AC)	Comparison of two groups: 55 subjects treated with oflox IV 400 mg twice daily followed by 55 subjects with oral oflox 400 mg twice daily were compared with 53 subjects treated with AS (1-2 g ampicillin / 0,5-1 g sulbactam four times daily) IV, followed by oral AC	Infection outcomes:  Clinically cured or improved,  Mean duration of therapy	No differences in outcomes between groups. Cured or improved 85% in oflox group vs 83% in AS/AC group.  Mean duration treatment: Oflox: 7.8 days (range, 1-25 days) i.v. followed by	Amputation: Toe/ray in AS n=7 vs in Cef n=7; below knee in AS n=1 vs in Cef n=1 Days of hospitalization: in AS 21.1 (range 6-58) vs in Cef 12.1 (range 4-39) (p=0.06)	1+	20 subjects were non-evaluable. Persistence of streptococci in oflox treatment group. Infected bone was supposed to be removed in those with osteomyelitis, but it was only removed in 71%. Numbers of subjects with	difference in "cure" as opposed to "cure + improvement"	Sponsored by Robert Wood Johnson Pharmaceutical Research Institute (now Johnson & Johnson Pharmaceutical Research and Development
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Lipsky 2004 (56)	RTC Multicentre Open label Study quality 4/9	371 enrolled, of whom 10 were not treated with antibiotics Prevalence of osteomyelitis 24% in linezolid (LZD) group vs	Comparison of two groups 241 subjects in the LZD group received 600 mg twice daily either iv or oral vs 120 subjects in AS group received 1.5-3 g four	Infection outcomes: Clinical cure	Clinical cure rates: Statistically equivalent (LZD: 81% vs. AS/AC: 71%). Subjects with LZD had a higher cure rate for infected foot	1-	Investigators diagnosed osteomyelitis in 77 subjects. The analysis of clinical outcome by pathogen is a modified intent-to-	Sponsored by Pfizer. One of two studies (the other is Lauf et al. (51)) to show higher
		group.	(500 mg amoxicillin/125 mg clavulanate three times daily).		oflox 13.2 days (range, 3-25 days) orally. AS: 7.1 days (range, 1-20 days) i.v. followed by AC 12.0 days (range, 1-24 days) orally. Subjects with osteomyelitis received mean duration oflox 9.2 days i.v. and 11.5 days orally vs. AS 7.0 days IV and AC 12.9 days orally		osteomyelitis do not seem to match in the tables	

		<p>17% ampicillin/sulbactam and amoxicillin/clavulanate (AS/AC) group,</p>	<p>times daily, or amoxicillin-clavulanate (AC) 500–875 mg 2–3 times daily).</p>	<p>Safety data</p>	<p>ulcers of 81% vs. AS/AC 68%; <math>p=0.018</math>. In cases without osteomyelitis, cure rates were LZD 87% vs. AS/AC 72%; (<math>p=0.003</math>).</p> <p>Subjects in LZD group had significantly more anaemia, thrombocytopenia and discontinuation of therapy than those in the AS/AC group. Any adverse event LZD: 26.6% vs AS/AC: 10.0% (<math>p&lt;0.01</math>)</p> <p>LZD: 17.2 ±7.9</p>	<p>treat population that consisted of subjects 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</p>	<p>incidence of adverse events in one treatment group</p>
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Lipsky 2005 (24)	RCT Multicentre Double blind Study quality 7/9	586 subjects with a diabetic foot infection classified as moderate-to-severe and requiring intravenous antibiotics Prevalence of osteomyelitis 8% in ertapenem group vs 6% in piperacillin/tazobactam group. Osteomyelitis	Comparison of two groups: 295 subjects received ertapenem (erta, 1 g daily iv) vs 291 subjects piperacillin/tazobactam (PT) (3.375 g every 6 hours iv) given for a minimum of 5 days, after which oral amoxicillin/clavulanate (875/125 mg every 12 hours) could be given for up to 23 days in either group.	of therapy	days (LZD iv: 7.8 ± 5.5 days, LZD oral 15.9 ± 7.4 days) AS/AC 16.5 ± 7.9 days (AS i.v. 10.4 ± 5.7 days, AC oral 15.0 ± 7.8 days).	1+	Dropout rate 23%, analysed by modified ITT. 12% of infections were leg ulcers. Data on site missing in 174. Proportion of clinical cure for organisms resistant to ertapenem ( <i>Pseudomonas</i> and enterococci) in subjects receiving that drug was similar to success	Sponsored by Merck Only an average of 11 days iv treatment duration was sufficient for these moderate to severe soft tissue infections. The clinical
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Lipsky 2007 (57)	RCT, Subanalyses of multicentre double-blind, double-dummy study	Original cohort of 617 subjects, hospitalized for skin or soft tissue infection, 127 of whom had a diabetic foot infection; of these 78 subjects with DFIs were available for treatment efficacy. Prevalence of osteitis 11% in moxifloxacin (moxi) vs 20% in piperacillin/tazobactam (PT) group. Bone infection was surgically “fully or partially	Comparison of two groups: Intravenous moxi (400 mg once daily), followed by moxi 400 mg once daily orally) vs PT (3.0/0.375 g every 6 hours) for at least 3 days, followed by amoxicillin-clavulanate (AC) (800 mg every 12 hours orally). Duration of treatment: moxi iv 6.7 days, oral 7.4 days, PT 6.3 days iv, AC 7.9 days oral	Infection outcomes: Clinical response of the infection at test-of-cure (TOC), 10-42 days post-therapy, Pathogen eradication	group (no significant differences) Clinical cure rates at TOC were similar for moxi (68%) and PT/AC (61%) (p=0.54). Overall pathogen eradication rates in the microbiologically -valid population were 69% for moxi versus 66% for PT/AC (p=1.0). No differences in safety outcomes	1++	Subjects with osteomyelitis were excluded if the bone could not be fully or partially resected	Sponsored by Bayer  Short duration of total treatment
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Lauf 2014 (51)	Substudy in subjects with osteomyeli- tis of the study mentioned above in the section on skin and soft tissue infection				Adverse events	No difference between groups (p=0.55)	antibiotics for 48h prior to inclusion despite having "severe" infection	
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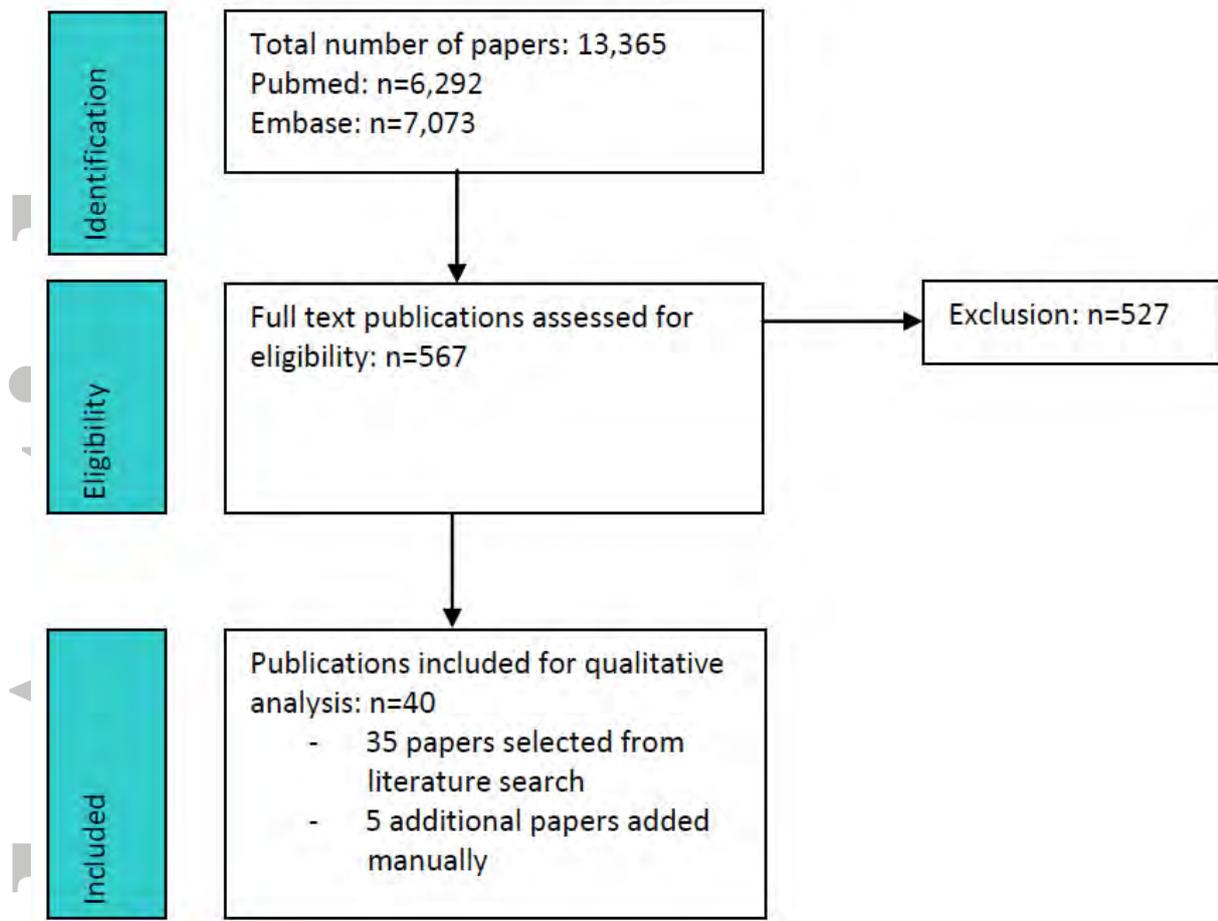


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included articles published before June 2014

Accepted