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SUPPLEMENT ARTICLE

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

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Abstract

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 a treated and a control population 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 articles meeting our criteria that were published since the 33 identified with the previous search, making a total of 40 articles from the world literature.
The identified articles included 37 randomised controlled trials (RCTs) and three 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 1 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 with that of 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 and osteomyelitis in diabetic patients. Copyright © 2015 John Wiley & Sons, Ltd.

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, UK) [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 Online 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 article 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' contributed 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 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 article 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 (Online Tables S1–9).

Results

The literature search identified a total of 13 365 articles (6292 from PubMed and 7073 from Embase), of which 5848 were published between July 2010 and July 2014. Figure 1 summarises the flow diagram of the review process of all articles published by June 2014. After review of all titles and abstracts, 567 articles 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 RCTs and five were cohort studies. One article was actually a description of two studies in one publication [17]. With the exception of one Chinese study, all articles selected for data extraction were published in English. In some articles, patients with diabetes and a DFI formed a subgroup, for example, from among patients with various skin and soft tissue infections (SSTI). We excluded these studies if insufficient

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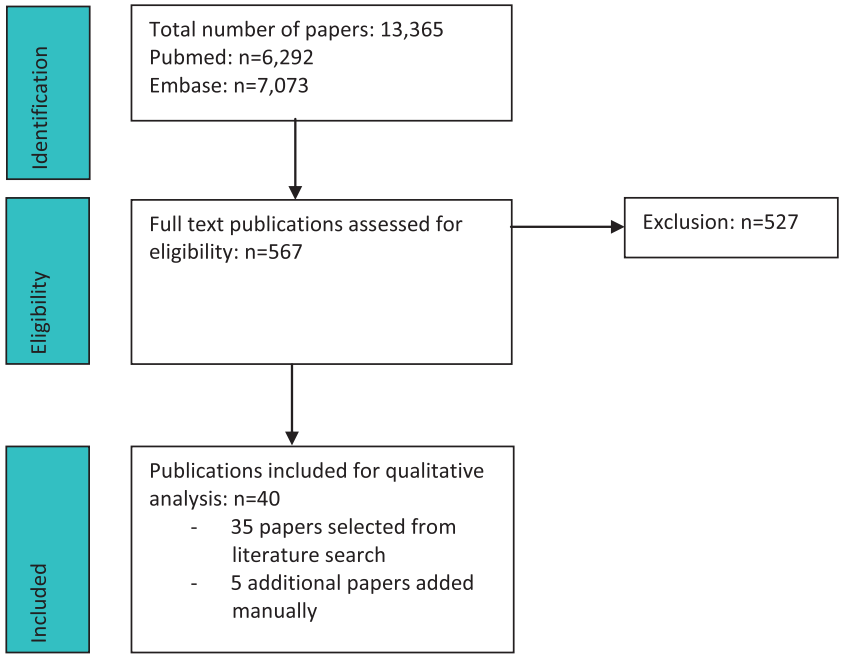

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of included articles published before June 2014

detail was provided specifically on the diabetic foot subpopulation. Fourteen studies reported on the use of antibiotics in SSTI. 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 an SSTI. 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 on hyperbaric oxygen treatment (HBOT).

Interventions for treatment of DFIs, by selected topics

Early surgery in the management of infection (Table S1)
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 were 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 [20,21].

Economic aspects of antibiotic choice (Table S2)
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], the authors reported a total potential cost saving of $US61 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 $US6.

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Topical negative pressure wound therapy (Table S3)
In the single article 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 S4)
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 with that of 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 povidione 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 30 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 h 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 [17,29].

Granulocyte-colony stimulating factor (Table S5)
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 S6)
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 10 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].

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Hyperbaric oxygen therapy (Table S7)

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 (Table S8)

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 with 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 2 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 1 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 cephalexin [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 SSTI 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 2 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 h [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 SSTI, but the authors included a planned substudy in subjects with osteomyelitis that we discuss subsequently. 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

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of adverse events and the 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 SSTI in the foot of individuals with diabetes is that the treatments compared were broadly equivalent (Table S1). 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 S9)

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 2 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 1 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]; cefoxitin [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 earlier in the section on Skin and soft tissue infection [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 SSTI 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 cefoxitin 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 cefoxitin-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 [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 (Table S1), of these studies was generally good, and each reported no significant difference in

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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 articles that met our inclusion criteria, only seven of which were published in the last 4 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 articles.

Conflicts of interest

B. A. L.: Research funding from Innocoll; consulting for Innocoll, Merck, Pfizer, Dipexium, Cubist, Cerexa, KCI/Acelity;

L. L. 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.

E. S.is a speaker and received congress support from Sanofi-Aventis and Novartis; consulting and received congress support from Pfizer; and a consultant for Cubist;

E. J. P., J. A. S., E. J. B., M. D., J. E., S. K., S. V. A., V. U. R., and W. J.: none declared.

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Supporting information

Tables S1–S9 (evidence tables) and the search strategy can be downloaded as supplements from the publisher's website.

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