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SUPPLEMENT ARTICLE

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

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Abstract

The optimal approaches to managing diabetic foot infections remain a challenge for clinicians. Despite an exponential rise in publications investigating different treatment strategies, the various agents studied generally produce comparable results, and high-quality data are scarce. In this systematic review, we searched the medical literature using the PubMed and Embase databases for published studies on the treatment of diabetic foot infections as of June 2018. This systematic review is an update of previous reviews, the first of which was undertaken in 2010 and the most recent in 2014, by the infection committee of the International Working Group of the Diabetic Foot. We defined the context of literature by formulating clinical questions of interest, then developing structured clinical questions (PICOs) to address these. We only included data from controlled studies of an intervention to prevent or cure a diabetic foot infection. Two independent reviewers selected articles for inclusion and then assessed their relevant outcomes and the methodological quality. Our literature search identified a total of 15 327 articles, of which we selected 48 for full-text review; we added five more studies discovered by means other than the systematic literature search. Among these selected articles were 11 high-quality studies published in the last 4 years and two Cochrane systematic reviews. Overall, the outcomes in patients treated with the different antibiotic regimens for both skin and soft tissue infection and osteomyelitis of the diabetic foot were broadly equivalent across studies, except that treatment with tigecycline was inferior to ertapenem (±vancomycin). Similar outcomes were also reported in studies comparing primarily surgical and predominantly antibiotic treatment strategies in selected patients with diabetic foot osteomyelitis. There is insufficient high-quality evidence to assess the effect of various adjunctive therapies, such as negative pressure wound therapy, topical ointments or hyperbaric oxygen, on infection related outcomes of the diabetic foot. In general, the quality of more recent trial designs are better in past years, but there is still a

Abbreviations: GRADE, grading of recommendations, assessment, development and evaluation; DFI, diabetic foot infections; DFO, diabetic foot osteomyelitis; G-CSF, granulocyte-colony stimulating; HBOT, hyperbaric oxygen treatment; IWGDF, International Working Group on the Diabetic Foot; NICE, National Institute for Health and Clinical Excellence; NPWT, negative pressure wound therapy; PICO, structured clinical question; SSTI, skin and soft tissue infection.

great need for further well-designed trials to produce higher quality evidence to underpin our recommendations.

KEYWORDS
antibiotics, diabetes mellitus, diabetic foot infection, osteomyelitis, surgery, systematic review

1 | INTRODUCTION

Diabetic foot infections (DFIs) are associated with considerable morbidity, a worsened 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, there have been four published systematic reviews of studies of different treatment modalities of DFIs.[2-6] One of these was restricted to studies of subjects with osteomyelitis affecting the foot in diabetes,[2] while the others included skin and soft tissue as well as osteomyelitis in the diabetic foot.[3-6] Of the latter reviews, two were conducted under the auspices of the International Working Group on the Diabetic Foot (IWGDF)[3,4] and the other by the National Institute for Health and Clinical Excellence (NICE, United Kingdom).[5,6] Other groups have published guidelines on DFIs as well, but these were not based on a systematic review of literature.[7-10] There have been several systematic reviews on specific types of interventions (eg, systemic antibiotics,[11] topical antimicrobials,[12] and granulocyte-colony stimulating factor[13]), that we will mention later in this review. The present report updates and, by consolidating the results of previous and current literature searches, replaces the International Working Group on the Diabetic Foot (IWGDF) systematic review of treatment of DFI conducted in 2015 and published in 2016.[4] The review focuses on studies of all types of therapeutic interventions that could help inform the working group on developing recommendations for the IWGDF guideline on diagnosis and treatment of DFI.[14] This review does not focus on definitions of infection or on methods for diagnosis.

2 | METHODS

The IWGDF appointed a working group composed of 12 international experts in the field to conduct the work of formulating this review. We performed the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the consensus and checklist on updating systematic reviews.[15,16] We entered the systematic review in the PROSPERO database for systematic reviews in 2014, under number CRD42018102925. We defined the population of interest (P), interventions (I), comparator (C), and outcomes (O), from which we formulated clinical questions (PICOs). The IWGDF Editorial Board and 13 external experts from various countries reviewed drafts of the document for accuracy and clinical relevance.

2.1 | Population

Persons aged 18 years or older, with diabetes mellitus (of any type) who have an infection of the foot (diagnosed by any clinical, laboratory, or imaging methods) that involves skin, soft tissue, bone, or other structures, caused by any microorganism.

2.2 | Interventions

We reviewed any study of an intervention (eg, antibiotic, antiseptic, surgery, and adjunctive therapy) to prevent or cure infection in a diabetic person's foot.

2.3 | Comparator

In addition to the subjects who received a specific intervention, all included studies had to have a contemporaneously studied set of subjects who received a control intervention. The control intervention could be a placebo, a sham-device or sham-procedure, a type of intervention or medicine different from the index intervention, no therapy, or usual clinical care.

2.4 | Outcomes

We only included outcomes that were relevant to an infectious aspect of the diabetic foot. These could include clinical cure of infection, requirement for lower extremity amputation, occurrence of a new infection, death, hospitalization, resolution of a foot ulcer, eradication of microbial pathogens, quality of life, adverse effects, or cost of treatment.

2.5 | PICOs

The PICOs we used to define the context of the literature search were as follows:

- Which persons presenting with diabetes and a foot infection should be hospitalized for management of infection?
- In a person with diabetes and a foot infection, is any particular antibiotic regimen (specific agent[s], route, duration) better than any other for treating soft tissue or bone infection?
- In a person with diabetes and osteomyelitis of the foot, are there circumstances in which non-surgical (antibiotic only) treatment is

as safe and effective (in achieving remission) as surgical treatment (combined with antibiotic therapy)?
- In a person with diabetes and a foot infection, does the addition of any specific adjunctive treatment to systemic antibiotic therapy improve resolution of clinical findings of infection or accelerate wound healing?

After the literature search was performed, the PICOs underwent minor textural changes and are therefore slightly different from the PICOs used in the guideline document.[14]

2.6 | Context

On June 30, 2018, we searched both the PubMed and the Excerpta Medica (Embase) databases using the string described in Appendix S1. This was the same search string as the one we employed in 2015. The search string was designed to identify: all prospective and retrospective studies, in any language, that evaluated interventions for the treatment of foot infections in the given population and that were published between June 30, 2014 and June 30, 2018. We combined the results of this literature search with the results of the earlier systematic review conducted in 2015.[4]

Eligible studies included systematic reviews, randomized controlled trials (RCTs), case-control studies, prospective and retrospective cohort studies, interrupted time series (ITS), or controlled before-and-after (CBA) design studies. We only included a systematic review when all publications it included met our inclusion criteria. 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 and analysed. We excluded case reports, uncontrolled case series, studies with non-concurrent controls, as well as studies that were not related to treatment of DFIs. We also searched the ClinicalTrials.gov (https://clinicaltrials.gov) and the World Health Organization (WHO)-International Clinical Trials Registry Platform (ICTRP) trial registries (http://apps.who.int/trialsearch/default.aspx) for studies that appeared to meet our criteria. For studies of potential interest, we made an attempt to contact the designated investigator for outcome results, but we included no study identified by this process. We searched conference proceedings whose title and abstract suggested they might be appropriate for inclusion in our review; our plan was that if we did not find a full-article copy of a study that seemed promising, we would contact the authors for more information to assess for any possible publication bias or selective reporting of results, but this was not needed.

One author assessed the title and abstract of each study identified by the search string to see if it likely met our eligibility criteria. For potentially eligible publications, pairs of authors independently reviewed the full, published article to assess whether or not it met our 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.[17] 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.

We translated the methodological quality score into a level of evidence using the Scottish Intercollegiate Guidelines Network (SIGN) instrument as either level 1 [systematic reviews or randomized controlled trials (RCTs)] or level 2 (case-control, cohort, CBA, or ITS studies).[18] 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, the interventions, and follow-up and outcomes, we made no attempt to pool the results of the included studies. We compiled the evidence tables following collective discussion (see Appendix S2).The group of authors drew conclusions for each intervention based on the strength of the available evidence, formulated as evidence statements and accompanying assessment of the quality of the evidence, according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE).[19] All members of the working group discussed these evidence statements until they reached consensus.

3 | RESULTS

The literature search from PubMed and Embase identified a combined total of 15 327 articles, of which 1962 were published since the previous IWGDF systematic review (ie, between July 2014 and July 2018). Figure 1 summarizes the flow diagram of the review process of all articles published by July 2018. After review of all titles and abstracts, we selected 626 articles for full text review. Of these, only 48 met the eligibility criteria for inclusion. We added five additional older studies that we identified by means other than the systematic literature search.[20-24]

3.1 | Types of studies

Of the 53 included studies, 13 were published between 2014 and 2018.[11,12,25-35] Among these 53 studies, 42 were RCTs (of which seven were published after the search in the last IWGDF systematic review in 2015), six were cohort studies (of which one was published after 2015[35]), and three were case-control studies (all published after 2015). One article was actually a description of two studies in one publication.[36] Two articles published after 2015 were Cochrane reviews.[11,12] With the exception of one Chinese study (that was translated into English), all articles selected for data extraction were published in English. In some articles patients with diabetes and a DFI formed a subgroup of the total study population, for example, from among patients with various skin and soft tissue infections (SSTIs). We included these studies only if the authors provided sufficient detail specifically on the subpopulation with a DFI. Sixteen studies, of which two were published since the last IWGDF systematic review of

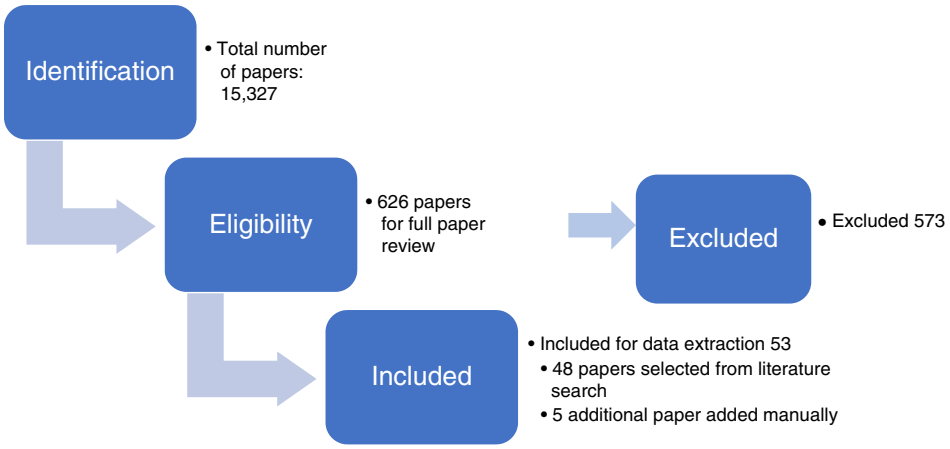

FIGURE 1 Flow diagram of included articles of papers

interventions for DFIs,[29,32] reported on the use of antibiotics in SSTI. Eleven original research studies and one Cochrane review[11] were in patients with for whom DFIs included osteomyelitis; among these, one study was on the use of bone biopsy, another was a substudy of patients with exclusively soft tissue infections, and two were on surgery in diabetic foot osteomyelitis. Seven studies, of which three were published since the last IWGDF intervention systematic review,[26-28] reported on treatment with topical antiseptic agents. Four published randomized studies (of which two were published since the last systematic review)[30,31] and a recent Cochrane review[12] assessed the use of topical antibiotic therapy, used either alone or in combination with systemic antibiotic treatment, for a diabetic foot SSTI. Two studies reported on outcomes of alternative or folklore treatments of DFI.[33,34] Five studies, of which one was recently published,[35] reported on the role of surgery in treating DFI. Two studies dealt with the financial costs of different antibiotic regimens. We identified five studies on the value of granulocyte-colony stimulating factors (G-CSF), two studies (of which one was a published after 2015[25]) on negative pressure wound therapy (NPWT), and one study identified in the earlier systematic review on hyperbaric oxygen treatment for DFIs.

3.2 | Interventions for treatment of DFIs, by PICO

3.2.1 | PICO

Which persons presenting with diabetes and a foot infection should be hospitalized for management of infection?

Summary of literature

Hospitalization is an expensive and limited resource that is required for some, but not all, patients with a DFI. The decision on who requires hospitalization is sometimes based on local health care resource issues, but most often, it is determined by the patient's clinical characteristics. Certainly, it is best to admit patients to hospital who need in-patient services (eg, intravenous administration of antibiotics, surgery, metabolic stabilization, urgent diagnostic procedures, and nursing care), but many patients in published studies are successfully treated on an ambulatory basis. We did not identify any studies that directly compared outcomes between subjects treated in hospital versus as outpatients. Also, we found no studies that identified specific features that could predict which patients needed to be treated in hospital or on outpatient basis. In most studies, it was not clearly stated where patients were treated, but the majority seemed to be treated on inpatient basis initially with intravenous antimicrobial therapy, followed by oral outpatient antibiotic therapy. One study explicitly enrolled only subjects treated entirely on an outpatient basis,[37] while others enrolled only subjects treated entirely in hospital.[38,39] Although these groups of subjects might not be comparable, they seemed to achieve comparable results.

Evidence statement

Differences in outcomes of patients treated in inpatient or outpatient setting have not been adequately studied. Because of a lack of comparative study, the criteria for choosing inpatient versus outpatient care of subjects with a DFI remain unclear.

Quality of evidence

Low.

References

None.

3.2.2 | PICO

In a person with diabetes and a foot infection, is any particular antibiotic regimen (specific agent[s], route, duration) better than any other for treating soft tissue or bone infection?

Skin and soft tissue infection, summary of literature

Topical treatment with antibiotics. Our review identified five RCTs[30,31,36,40-42] and one systematic review[12] on treatment of DFI with topical antimicrobial agents. The Cochrane systematic review included 22 articles and concluded that there was little difference in the rate of treatment-related adverse events with topical versus systemic antibiotic therapy, but no evidence of difference between the various compared treatments.[12] The Cochrane review had slightly

different search criteria than our systematic review, and we updated it with other more recently published articles. One RCT compared the results of treatment with a topical application of the antimicrobial peptide pexiganan versus treatment with an oral antibiotic (ofloxacin).[36] 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, while the incidence of adverse events was higher in the ofloxacin group. Despite these promising results, a recent large unpublished (except for a summary in ClinicalTrials.gov) study of topical therapy for a mild DFI with pexiganan found that it was not superior to placebo (standard of care treatment alone).[41,42]

Three RCTs compared the value of adjunctive treatment with a gentamicin-collagen sponge placed on the infected wound to systemic antimicrobial therapy in patients with a mild,[30] moderate,[40] or moderate and severe DFI.[31] All participants received standard wound care, and in the two studies of moderate and severe infections, they all received systemic antibiotic therapy, but half were randomized to also receive the gentamicin-collagen sponge.[30,31,40] In the mild infection study, pathogen eradication was high in both groups, and they recorded no adverse events.[30] Unfortunately, this single-blinded, single-centre study was underpowered because they had difficulty in enrolling enough subjects to reach the calculated statistical power.[30] The sponge was well-tolerated, but there was no difference in either clinical or microbiological outcomes between the two groups.[30] In the study of 88 subjects with moderate and severe infections, the authors found non-significant differences in clinical cure and pathogen eradication.[31] In the study of moderate DFIs, the clinical cure rate for subjects in the gentamicin-collagen sponge group was worse than subjects in the control group at treatment day 7 (the designated primary outcome), but significantly better 2 weeks after discontinuing treatment.[40] The study was marred by a modification of the selection criteria (to enhance enrolment) during the study, failure to reach the recruitment target, and a high withdrawal rate, making it difficult to interpret the reported findings. All subjects in the studies tolerated the gentamicin-collagen sponge well.

Systemic treatment with antibiotics. The bulk of the published 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 13 RCTs, one cohort study and one systematic review[11] that compared new products in the management of diabetic foot SSTI of varying severity with other commonly used antibiotic regimens, including (in roughly historical order) ceftriaxone versus cefazolin[43]; clindamycin versus cephalexin[37]; clinafloxacin versus piperacillin/tazobactam[44]; ertapenem versus piperacillin/tazobactam[23,32]; levofloxacin versus ticarcillin/clavulanate[22]; ceftriaxone plus metronidazole versus ticarcillin/clavulanate[45]; ceftriaxone versus quinolones[46]; piperacillin/tazobactam versus ampicillin/sulbactam[47]; daptomycin versus a semi-synthetic penicillin or vancomycin[48]; ceftobiprole versus vancomycin plus ceftazidime[49]; moxifloxacin versus amoxicillin/clavulanate[50]; moxifloxacin versus piperacillin/tazobactam[51]; and tigecycline versus ertapenem with or without vancomycin.[52] Only one of these was published after 2015[32] and thus not included in the previous systematic review.

In studies that provided the details, the mean duration of administration of the antibiotics in subjects with SSTI ranged from 5 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.[37] Although we did not identify studies that directly compared different durations of antibiotic therapy, the aggregate data suggest that a 2-week duration of antibiotic treatment is likely sufficient to treat SSTI in the foot of patients with diabetes mellitus. Clinical cure rates in the various studies (for patients without osteomyelitis) ranged from 48%[44] to 97%.[32]

With notable exceptions (mostly more recently performed studies[32,51,52]), many of the studies were weakened by suboptimal 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-day duration) DFI of any severity that required hospitalization and initial parenteral antibiotic treatment for at least 48 hours.[51] 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 (alone) and ertapenem (with or without the addition of vancomycin) in hospitalized subjects with an acute DFI of any severity.[52] The primary study enrolled subjects who had only SSTI, but the authors included a planned substudy in subjects with osteomyelitis that we discuss below in the osteomyelitis section. 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 subjects of clinically evaluable or 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.

The third high-quality study was a non-inferiority, multicentre trial of ertapenem versus piperacillin/tazobactam (with or without the addition of vancomycin in either group) in 565 subjects with moderate or severe DFIs without osteomyelitis.[32] Infection was defined as: purulent drainage or three or more of the following: fever (temperature ≥ 38.5°C); elevated white blood cell count (>10,000/mm^3) with greater than 5% band neutrophils; periwound oedema, erythema, tenderness, or pain; fluctuance, warmth, or induration; or lymphangitis with a skin lesion. The wound penetrated to bone in 71 subjects, but those in whom osteomyelitis was not surgically removed were excluded. Subjects were treated for 5 to 28 days and could be switched to oral therapy with amoxicillin/clavulanate when deemed appropriate. There was no significant difference in the rates of favourable clinical or microbiological responses between the two

groups after 10 days of follow-up, except that subjects with greater than or equal to two criteria of the systemic inflammatory response syndrome (ie, a severe infection) had a slightly higher favourable clinical outcome (91% vs 97%, $P < 0.04$) in the piperacillin/tazobactam group. The findings suggest that ertapenem was clinically non-inferior to piperacillin/tazobactam in patients with moderate or severe DFIs. Although the study was not powered to detect statistical differences between study treatments in the severe DFI stratum, in the subset analysis, subjects with a severe DFI treated with ertapenem had a significantly lower clinical resolution rate at discontinuation of treatment compared with subjects treated with piperacillin/tazobactam [91.5% vs 97.2% (119/130 vs 139/143), $P = 0.04$]. We can draw no conclusions from this observation as the study was designed for non-inferiority, and it was not powered for the analysis of subjects in the severe infection subgroup. Analysis in the modified intention to treat population showed comparable clinical response rates between the two groups. There were no significant differences in adverse events in the ertapenem group compared with the piperacillin/tazobactam group. In another non-inferiority trial comparing ertapenem to piperacillin/tazobactam in subjects with DFIs (SIDESTEP) published in 2005, the authors used similar definitions for infection as in the study by Xu et al. The proportion of subjects with a favourable clinical response at the primary endpoint (the discontinuation of antimicrobial treatment), adjusted for baseline severity, was 94% (213 of 226) for the ertapenem group and 92% (202 of 219) for the piperacillin/tazobactam group. Among the 574 patients in the modified intention to treat analysis, the proportion with a favourable clinical response at the 10-day of follow-up was 71% (206 of 289) and 66% (188 of 285), in the ertapenem and piperacillin/tazobactam groups, respectively (treatment difference 5%, 95% CI −2.6 to 12.5). None of these differences between the treatment groups is statistically significant. Based on the primary endpoint of these two large, well-designed RCTs, we concluded that ertapenem is non-inferior to piperacillin/tazobactam for treating DFIs.[32,53]

A 2015 Cochrane systematic review of systemic antibiotics for treating DFI included 20 trials and concluded that it was unclear if any one treatment is better than others either in resolving infection or in safety.[11] Similarly, 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 (see Appendix S2). The one instance in which equivalence was not demonstrated was in the large, well-designed evaluation in which tigecycline was inferior to ertapenem ± vancomycin.[32,52]

The published studies of antimicrobial therapy that we selected for review predominantly used agents that targeted commonly isolated gram-positive bacteria and often covered usual gram-negative bacteria and sometimes obligate anaerobes. In some included studies, there was no specific empiric therapy chosen to target *Pseudomonas*.[37,43,48,50,52] In the studies that did compare outcomes of specific (empirical) agents that did or did not cover *Pseudomonas*, there was no significant difference in outcomes.[23,32,45-47,51] In two other studies, the empiric antibiotics used specifically targeted gram-positive microorganisms in both the intervention and the comparator arms (viz clindamycin vs cephalexin,[37] and daptomycin and a semisynthetic penicillin or vancomycin.[48]) In only one study was a first generation cephalosporin (with predominantly anti-gram-positive activity) compared with a third-generation cephalosporin (with an antibacterial spectrum that includes gram-negative organisms).[43] There were no differences in outcome between the two treatment arms, but because of flaws in design and conduct, this is a low quality study.

None of these studies was the primary objective to compare empiric treatment of gram-positive versus gram-negative (or obligately anaerobic) microorganisms. In most of these studies, it was not possible to determine if there was any effect of infection with a specific bacterial species (eg, *Pseudomonas aeruginosa*) on the outcome of infection.

The choice of empiric antibiotic treatment usually depends largely on the local prevalence, and antimicrobial resistance patterns, of bacteria involved in diabetic foot (and other types of) infections. The prevalence of pathogens and their antibiotic resistance patterns vary among different geographical locations. In studies of DFI, we could not identify those that specifically looked at outcomes of empiric antimicrobial therapy selected based on knowledge of local prevalence and resistance patterns of microorganisms.

Osteomyelitis

We identified 11 studies conducted in patients with diabetic foot osteomyelitis. One study included results on the value of bone biopsy,[54] another was a substudy of patients with soft tissue infections.,[52] and another was an RCT of 6 versus 12 weeks of antibiotic therapy without surgery.[29,35,55,56]

We identified one cohort study that addressed the question of whether or not using a percutaneous bone biopsy and an antibiotic regimen containing rifampicin for gram-positive organisms would help improve outcomes in primarily non-surgical management of diabetic osteomyelitis of the foot (DFO).[54] Among 50 subjects, 32 had had previous unsuccessful treatment for osteomyelitis. The rate of remission of infection was significantly higher in the group treated with an antibiotic regimen that, based on bone culture results, included rifampicin than in those treated with antibiotic regimens without rifampicin and who did not undergo bone biopsy [82% vs 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 complicated by osteomyelitis, either exclusively or as part of a described subset.[20,52,53,57-61] Seven of these RCTs compared the use of a beta-lactam/beta-lactamase inhibitor combination antibiotic against one of the following agents: imipenem/cilastatin,[20,57] cefoxitin,[58] ofloxacin,[59] linezolid,[60] ertapenem,[53] or moxifloxacin.[61] The number of subjects with osteomyelitis included was low (<10%) in two studies[53,59] but substantial in the other six that we included. Some form of debridement, often including resection of infected bone, was frequently performed in all studies comparing antibiotic regimens. The clinical cure rate, although variously defined, was

exceptionally low in both subject groups in one study,[58] but ranged from 61%[61] to 94%[54,57] in others. Mean duration of antibiotic treatment was surprisingly short, ranging from 6[58] to 42 days,[52] likely related to the high percentage of subjects that underwent (partial) bone resection. Results of each of these studies reported no significant differences in outcomes among the different antibiotic regimens. Two other studies did report differences in an outcome.[52,58] 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 SSTI section).[52] After a follow-up of 25 to 27 weeks, the ertapenem ± vancomycin treated group had statistically non-significant higher cure rates. As in those with just SSTI, there was a significantly higher rate of adverse events in the tigecycline treated group in this study. The authors did not mention if the infected bone was always surgically removed in the osteomyelitis substudy. In the other single-centre, double-blind study, 36 subjects were treated with either cefoxitin or ampicillin/sulbactam.[58] There were more subjects with DFO in the ampicillin/sulbactam group compared with the cefoxitin group (44% vs 28%, respectively). Subjects in the cefoxitin group had a significantly higher rate of "cure" (defined as complete alleviation of signs or symptoms of infection) than subjects in the ampicillin/sulbactam group, although cure rates in both groups were notably lower than in other studies comparing antibiotics. The low cure rates might reflect the short duration of antibiotic treatment (6 days). The outcome of treatment was "cure or improvement" (ie, those with complete and those with incomplete alleviation of signs and symptoms of infection) in 15 of 17 of the ampicillin/sulbactam treated patients and in 16 of 17 of the cefoxitin treated patients. There was no difference in microbiological outcomes, days of hospitalisations, or number of amputations.

Only a few studies specially mention data on duration of antimicrobial therapy. In three studies of predominantly surgical versus antibiotic therapy, the investigators prescribed antibiotics for a duration of up to 10 days versus 90 days in the RCT,[55] mean of 45 and 48 days in one of the cohort studies,[56] and mean of 10 and 11 weeks, median 5 weeks (range 2 to 44 weeks) and 8 weeks (range 6 to 52 weeks) in the other cohort study[35] in the surgical and antibiotic group, respectively.

We identified one recent small, but well-designed, RCT aiming to determine if 6 versus 12 weeks of antibiotic treatment in subjects without peripheral artery disease treated conservatively led to better outcomes.[29] Twelve of 20 subjects in the group that was treated with 6 weeks versus 14 of 20 in the group treated 12 weeks achieved remission ($P = 0.5$). Gastrointestinal adverse events were less common in the group treated for 6 weeks, than in the group treated for 12 weeks (15% vs 45%, respectively, $P = 0.04$). To our knowledge, this is the only study that directly compared two treatment durations in subjects with DFO. This study suggests that 6 weeks of treatment is sufficient for patients with forefoot DFO who do not need to undergo surgery for its treatment.

The quality of most, but not all (see Appendix S2), of these studies was generally good and each reported no significant difference in outcome between the treatment arms. None of the studies specifically commented on differences in outcomes between oral and parenteral routes of administration. In most of the RCTs of antibiotic treatment of antibiotics, however, the authors prescribed parenteral antibiotics followed by a switch to oral antibiotics. One non-inferiority RCT that was published after the inclusion dates of our systematic review, and was therefore not included in the search results, randomized subjects with a variety of severe osseous and joint infections, including approximately 20% subjects with diabetic foot osteomyelitis, to treatment with an oral versus a parenteral antibiotic regimen.[62,63] There were no significant differences in treatment outcomes between the two routes of therapy for the various types of infections combined. Unfortunately, the authors did not provide separate outcomes for subjects with DFO, which makes the results of the study hard to apply to the general population of persons with DFO.

Economic aspects of antibiotic choice

We identified two studies that compared economic aspects of different antibiotic regimens in the treatment of soft tissue DFIs. In one study, in males from United States (military veterans), among 22 subjects admitted to hospital there was a total potential cost saving of US $61 (2004 price, not corrected for inflation) per subject treated with once-daily ceftriaxone and metronidazole, compared with four times daily ticarcillin/clavulanate.[45] The other study,[38] a subgroup analysis of a larger RCT conducted in the United States,[53] reported the results of a cost-minimization 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 US $6 (2007 price, not corrected for inflation) higher.

Evidence statement. There were no differences in clinical outcomes among antibiotics compared in studies of DFIs, including diabetic foot osteomyelitis, except for one study that found that tigecycline was inferior to ertapenem.

Quality of evidence. High.

References. Bradsher and Snow[43]; Lipsky et al[37]; Siami et al[44]; Graham et al[22,23]; Xu et al[32]; Clay et al[45]; Lobmann[46]; Harkless et al[47]; Lipsky et al[48]; Noel et al[49]; Vick-Fragoso et al[50]; Schaper et al[51]; Lauf et al[52,53]; Saltoglu et al[20]; Lipsky et al[48]; Grayson et al[57]; Erstad and McIntyre[58]; Lipsky et al[59]; Lipsky et al[60]; Lipsky.[61]

Evidence statement. There is insufficient evidence to demonstrate that topical pexiganan cream is non-inferior to oral ofloxacin for mild or moderate diabetic foot SSTI or to placebo for mildly infected DFUs.

Quality of evidence. Moderate

References. Lipsky et al[36]; Clinicaltrialsgov[41,42]

Evidence statement. Treatment with a gentamicin-collagen sponge, whether compared with placebo for mildly infected DFUs or as

adjunctive therapy to systemic antibiotic therapy for moderate or severe DFIs, does not appear to improve outcomes.

Quality of evidence. Moderate.

References. Uckay et al[30];Uçkay[31]; Lipsky.[40]

Evidence statement. There is insufficient evidence to determine whether or not treatment for mild DFIs targeted at just gram-positive organisms lead to comparable results to treatment targeted at both gram-positive and gram-negative organisms.

Quality of evidence. Low.

References. Bradsher and Snow[43]; Lipsky et al[37]; Lipsky et al[48]; Vick-Fragoso et al[50]; Lauf et al[52]; Graham et al[23]; Xu et al[32]; Clay et al[45]; Lobmann et al[46]; Harkless et al[47]; Schaper et al.[51]

Evidence statement. There is no evidence to determine whether or not outcomes are better when empiric therapy is selected based on knowledge of local microorganism's antibiotic resistance patterns than empiric therapy without that knowledge.

Quality of evidence. Low.

References. None.

Evidence statement. Duration of antibiotic treatment for DFIs need not be longer than about 2 weeks in most cases of SSTI or 6 weeks in patients with osteomyelitis who do not undergo surgical resection of infected bone.

Quality of evidence. Moderate.

References. Bradsher and Snow[43]; Lipsky et al[37]; Siami et al[44]; Graham et al[22,23]; Xu et al[32]; Clay et al[45]; Lobmann[46]; Harkless et al[47]; Lipsky et al[48]; Noel et al[49]; Vick-Fragoso et al[50]; Schaper et al[51]; Lauf et al[52,53]; Saltoglu et al[20]; Lipsky et al[48]; Grayson et al[57]; Erstad and McIntyre[58]; Lipsky et al[59]; Lipsky et al[60]; Lipsky.[61]

Evidence statement. The antibiotic treatment related costs of therapy with ceftriaxone ± metronidazole versus ticarcillin/clavulanate and of ertapenem versus piperacillin/tazobactam for diabetic foot infections are only marginally different.

Quality of evidence. Low.

References. Clay et al[45]; Tice et al[38]

Evidence statement. In published treatment studies, where bone was often surgically removed, the clinical cure rate of DFO ranged from 61% to 94%.

Quality of evidence. Moderate.

References. Saltoglu et al[20]; Lipsky et al[53]; Lauf et al[52]; Grayson et al[57]; Erstad et al[58]; Lipsky et al[59]; Lipsky et al[60]; Lipsky et al.[61]

Evidence statement. For treating DFO, antibiotic therapy delivered predominantly by the oral route (after about a week of intravenous therapy) is not inferior to therapy delivered predominantly by the intravenous route.

Quality of evidence. Low.

References. Saltoglu et al[20]; Lipsky et al[53]; Lauf et al[52]; Grayson et al[57]; Erstad et al[58]; Lipsky et al[59]; Lipsky et al[60]; Lipsky et al[61]; Lázaro-Martínez et al[55]; Ulcay et al[56]; Tone et al,[29] Li et al[62]

3.2.3 | PICO

In a person with diabetes and osteomyelitis of the foot, are there circumstances in which non-surgical (antibiotic only) treatment is as safe and effective (in achieving remission) as surgical treatment (combined with antibiotic therapy)?

"Early" surgery in the management of infection

Our search identified two single-centre studies that investigated the effect of treatment with "early" surgery (variously defined, but usually within 72 hours of presentation) versus delayed surgery, 3 to 6 days after admission in hospitalized patients with a severe, deep DFI, with or without osteomyelitis.[39,64] Around a third of subjects in both studies had osteomyelitis (defined by abnormalities on plain X-ray). Both studies found that there was a significant reduction in the rate of major lower extremity amputation in the early surgery group: from 27% to 13% in one study[39] and from 8 to 0% in the other.[64] Both studies, however, were limited by a high risk of bias, especially including a lack of randomization of the subjects and lack of standardized protocols for surgical (or medical and antimicrobial) treatment. Studies designed to answer questions about the role of surgery typically pose particular difficulties, such as selecting similar patients, standardizing operative techniques, and post-operative care.

Surgical versus non-surgical treatment of DFO

Other studies comparing predominantly surgical versus antibiotic therapy for treatment of DFO included one RCT[55] and two retrospective cohort studies.[35,56] The RCT compared predominantly surgical treatment versus non-surgical (antibiotic) treatment for DFO in a single-centre study with 52 subjects. Although it was not an inclusion requirement, all of the enrolled patients had osteomyelitis of the forefoot. Patients randomized to antibiotic therapy were treated until ulcer healing but to a maximum of 90 days; those randomized to surgery underwent removal of only the infected bone, without amputation, combined with only 10 days of systemic antibiotic therapy.[55] Limitations of the study included the fact that only a small percentage

of evaluated patients were enrolled, all subjects had DFO located in the forefoot, the presence of osteomyelitis was not diagnosed by bone biopsy in all the subjects treated medically, and subjects were excluded if they had a severe infection, necrotizing tissue infection, bone exposed in the base of the ulcer, kidney injury, or peripheral artery diseases. The results demonstrated no statistically significant differences between the two treatment groups in achieving wound healing, time to healing, ulcer recurrence after 12 weeks of follow-up or treatment related complication rates. Notwithstanding its limitations, the study results suggest that for appropriately selected patients, outcomes of treatment of DFO with predominantly surgical therapy compared with exclusively antibiotic therapy are similar.

A recent French/Spanish cohort study in 74 subjects with *Staphylococcus aureus* DFO compared treatment with either bone surgery with a short course of antibiotics or with more prolonged antibiotic therapy and bedside debridement.[35] Methicillin-resistant *S. aureus* was isolated from 23% of subjects in the surgery group compared with 46% in the predominantly antibiotic treated group. Outcomes were favourable in greater than or equal to 80% in both groups and not significantly different between them. Subjects in the antibiotic group were hospitalized significantly less often and for a shorter duration compared with those in the surgery group. The subjects in the predominantly antibiotic-treated group had a significantly longer duration of antibiotic treatment and more treatment related side effects than subjects in the surgery group. The other cohort study that compared outcomes of surgery versus antibiotic therapy for DFO was a retrospective review over 2 years of subjects hospitalized with predominantly forefoot DFO.[56] Among the 37 evaluable subjects, 15 were managed with antibiotic therapy (without surgery) and 23 with antibiotics and concomitant minor amputation surgery (undertaken at the bedside). The authors did not report the cure rates, but there were no significant differences between the groups in time to wound healing, duration of antibiotic administration, duration of hospitalization, or rate of recurrence (three in each group) 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.

Evidence statement. Early surgical debridement in patients hospitalized for an acute, severe DFI who need a surgical intervention (eg, to drain an abscess) appears to reduce the likelihood of a major lower extremity amputation.

Quality of evidence. Low.

References. Tan et al[39]; Faglia et al[64]

Evidence statement. Treatment with a primarily surgical or primarily non-surgical (antibiotic) approach in selected patients with forefoot DFO without peripheral artery diseases and without exposed bone or abscesses yields similar outcomes.

Quality of evidence. Medium.

References. Lázaro-Martínez et al[55]; Lesens et al[35]; Ulcay et al[56]

3.2.4 | PICO

In a person with diabetes and a foot infection, does the addition of any specific adjunctive treatment to systemic antibiotic therapy improve resolution of clinical findings of infection or accelerate wound healing?

Topical negative pressure wound therapy (NPWT)

We identified two studies that investigated the value of NPWT in patients with a DFI.[24,25] In one study, 130 subjects undergoing surgical debridement of an open wound or surgical dehiscence following minor amputation[24] were assigned to receive either NPWT or one of a variety of advanced dressings.[24] While healing was the main outcome, the authors also reported on an endpoint they called "infection control," determined by clinical evaluation (extent of granulation tissue, reduction in exudate, and visual aspects of the wound). They stated that when necessary they would take wound biopsies to assess "microbiological control," but provided no details on the results of these procedures. In this study, 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 the lack of critical study details, however, we could not assess the validity of the reported findings or draw conclusions about their usefulness.

The second study was a retrospective matched case-control, single-centre study that compared 10 subjects with progressive necrotising infection, who were treated with autologous bioengineered fibroblast grafts and negative pressure wound therapy, with 10 subjects who were treated with standard of care (surgical debridement, moist dressings, and autologous skin grafts).[25] Healing rates after 20 weeks were significantly higher, and recurrence rates lower, in the fibroblast/NPWT group, compared with the standard of care group (90% vs 29%, $P < .001$, and 20% vs 100%, respectively). There were no statistically significant differences in major amputations, graft take, or death.

Topical treatment antiseptics

Evidence statement. There is insufficient high-quality evidence to assess the effect of negative pressure wound therapy on infection-related outcomes in patients with a DFI.

Quality of evidence. Low.

References. Dalla Paola et al[24]; Armenio et al[25]

Topical treatment with antiseptic agents. Antiseptics are substances with antimicrobial action that can be applied topically but, in contrast

to antibiotics, cannot be administered systemically because of their toxic effects. They are often used either alone (for mild infections) or in combination with other (usually systemic) antimicrobial therapy (for moderate or severe infections). The effects of treatment with one such agent, superoxidized water, have been compared in three studies of patients with a DFI, to either soap or povidone iodine.[65-67] A small, single-centre RCT reported that compared with controls, treatment of a diabetic foot ulcer with superoxidized water was associated with less periwound erythema (a reduction of 81% vs 44%), less odour, and greater granulation tissue.[65] In a second study, non-blinded study among subjects who underwent surgery for a DFI, those treated with topical povidone iodine received systemic antibiotic therapy for a significantly longer duration compared with those treated with superoxidized water (15.8 days vs 10.1 days, $P = 0.016$).[66] Both studies provided data on long-term outcomes of wound healing, but neither specifically addressed the potential adverse effects of treatment with other topical disinfectants in the comparator groups.[65] The third study was an unblinded pilot RCT comparing the results of three treatment arms for 66 subjects with a mildly infected diabetic foot ulcer: topical superoxidized water alone, oral levofloxacin plus saline, and topical superoxidized water plus oral levofloxacin.[67] 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. Drawing conclusions from these three studies of superoxidized water treatment is limited by their weak trial designs, incomplete reporting, and possible sources of bias.

Three studies on other topical antiseptics have been published since our last systematic review.[26-28] An explorative, open, multicentre RCT with 40 subjects studied the effect on healing of infected diabetic foot ulcers of topical chloramines, an agent with presumed antiseptic effects and antibacterial properties, versus standard of care.[26] At 9 weeks, ulcers had healed significantly more often in the intervention group compared with the control group (7 vs 1, respectively, $P = .039$). Signs and symptoms of infection decreased during treatment in both groups, but there were no significant differences between the groups. More than 50% of subjects in each group received antibiotic therapy during the 12-week period of follow-up, but there were no significant differences between the groups. There were also no significant differences in the occurrence of adverse events between the groups. This study was limited by its open design and small sample size.

Another recent multicentre, parallel group, open label RCT with cross-over design compared outcomes of enzymatic debridement with clostridial collagenase ointment versus hydrocolloid gel in 215 subjects with an uninfected diabetic foot ulcer.[27] Wound closure rates, wound appearance, and need for debridement did not differ significantly between the two groups. Results of quantitative wound microbiology demonstrated that each ulcer harboured 1 to 5 bacterial species and wound infection occurred in 8.5% of subjects in the clostridial collagenase ointment group versus 13.8% of subjects in the hydrocolloid gel group (P calculated at 0.21).

A study published in 2014 described the results of a double-blind, placebo-controlled RCT on the effects of a single dose of photo-activated gel containing a novel cationic zinc phthalocyanine derivative (RLP068), developed as topical treatment for superficial bacterial and fungal infections, in subjects with an infected diabetic foot ulcer.[28] There was a significant and dose-dependent reduction in microbial load among 45 subjects randomized to one of three doses of RLP068 activated by exposure to red light but none in the 17 who received placebo.[28] There was also a non-significant reduction in IWGDF diabetic foot infection score in the photo-activated gel group, compared with the placebo group.

Another older study with 30 subjects with a diabetic foot ulcer compared the results of a single application of a topical antiseptic, either iodophor or rivanol, with a control group.[68] 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.

We identified additional studies of topical treatment with antibiotics that we have described in the section on SSTI.

Evidence statement. Some low-quality evidence suggests that treatment with topical superoxidised water can improve outcomes of diabetic foot infection.

Quality of evidence. Low.

References. Martínez-De Jesús et al[65]; Piaggesi et al[66]; Landsman et al[67]

Evidence statement. Separate individual studies of topical treatment with chloramines, clostridial collagenase ointment or a photo-activated gel containing cationic zinc phthalocyanine derivative suggest that there is insufficient evidence that these improve outcomes as an adjunct to treatment or prevention of diabetic foot infection.

Quality of evidence. Low.

References. Bergqvist et al[26]; Jimenez et al[27]; Mannucci et al.[28]

Evidence statement. There is insufficient evidence that topical treatment with rivanol or iodophor improve outcomes of treatment of diabetic foot infection.

Quality of evidence. Low.

References. Chen et al[68]

Natural or alternative remedies for diabetic foot infections

Cawich et al published studies investigating two natural remedies that are often applied by members of the local population to infected diabetic foot wounds in Trinidad and Tobago.[33,34] One case control study compared outcomes in 60 subjects who chose to

defer conventional medical attention and applied "soft candle" (hot paraffin drippings) to those in 382 subjects who initially sought conventional medical attention (free of cost) after discovering an infected diabetic foot ulcer.[33] For subjects in the soft candle group, compared with those that sought medical attention, mean length of hospitalization was 15.5 days versus 9.2 days ($P < 0.001$), and major amputation was undertaken in 13.3% versus 5.6% ($P = 0.048$), respectively. It is likely that these results reflect effects of treatment but may also be related to both the delay in medical care and possibly the lower socio-economic status of the subjects in the soft candle group. The other case control study from Trinidad and Tobago investigated outcomes of DFI in 96 subjects who elected to topically apply the "Wonder of Life Plant" (*Kalanchoe pinnata*) versus a group of 382 subjects that directly sought medical attention.[34] Analysis of the constituents of the leaves has demonstrated that at least one compound (saponin/bryophillin) has bacteriostatic effects against several bacteria. The authors excluded 225 patients who admitted to using other forms of non-medicinal therapy. In this study, there were no significant differences in the rate of major or minor amputations, or in-hospital mortality between the two groups.

Evidence statement. Subjects who had applied candle drippings on the wound had poorer outcomes than did those directly seeking medical care for a diabetic foot infection. There is no good evidence that topical treatment with Wonder of Life Plant (*Kalanchoe pinnata*) improves outcomes of treatment of diabetic foot infection.

Quality of evidence. Low.

References. Cawich et al[33]; Cawich et al[34]

Granulocyte-colony stimulating factor

We identified five single-centre RCTs,[21,69-72] and three systematic reviews (that also identified these RCTs)[13,73,74] examining the value of adjunctive use of granulocyte-colony stimulating factor (G-CSF) in DFIs,[21,69-72] We found no additional studies for this subject published since our last systematic review. Enrolled patients had only soft tissue infection in four of the five studies, and associated osteomyelitis in one.[71] 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 only one of the studies.[69] This latter study[69] also reported a shorter duration of intravenous antibiotic use in G-CSF-treated patients, but this was not observed in another study.[70] Hospital length of stay was shorter for the G-CSF group in two studies[21,69] but not in a third.[70] The percentage of patients who underwent surgical intervention was not statistically different between the two groups in the three studies that examined it[21,69,71] nor was the time to elimination of wound pathogens in two studies.[69,71] 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. The most recently published Cochrane systematic review and 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.[13]

Evidence statement

Adding G-CSF to standard treatment of DFI does not affect resolution of infection, healing of the wound, or the duration of systemic antibiotic therapy but does seem to reduce the likelihood of lower extremity surgical interventions (including amputation) and reduce duration of hospital stay.

Quality of evidence

High.

References

Viswanathan et al[21]; Gough et al[69]; Yönem et al[70]; de Lalla et al[71]; Kästenbauer et al[72]; Cruciani et al[13]

De Marco formula (a formulation of procaine and polyvinylpyrrolidone)

One observer-blinded, single-centre, RCT of 118 patients hospitalized with a DFI affecting an ischemic limb assessed the value of adding intramuscular injections of De Marco formula (0.15 mL/day of procaine and polyvinylpyrrolidone) for 10 days in addition to "conventional" therapy versus conventional therapy alone.[75] The 59 patients in each group were comparable in demographic and clinical characteristics. The cumulative percentage of unfavourable results (lower extremity amputation, predominantly major) was significantly lower in those treated with De Marco formula than those who were not (25.4% vs 45.8%; $P = 0.02$) and increased duration of treatment was directly related to favourable outcomes. It is hard to draw firm conclusions from the study, because interpretation of the results was severely limited by missing details. The same group published another study of De Marco formula on patients with an ischemic diabetic foot ulcer, but it contained no infection-related outcomes so did not add to the conclusions of the other report.[76]

Evidence statement. Low quality evidence suggests that the De Marco formula may reduce amputations in patients with an ischaemic diabetic foot infection.

Quality of evidence. Low.

References. Duarte et al[75]; Mesa et al[76]

Hyperbaric oxygen therapy. Although there have been several studies of the potential value of hyperbaric oxygen therapy (HBOT) for improving diabetic foot ulcer healing, we identified only one that

reported any 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 received no HBOT. At least some of the reported patients clearly had a DFI and all were treated with topical antiseptic and systemic antibiotic therapy. 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 study size, poor quality, and non-standardized methods, and non-standardized definitions used do not clearly support a benefit for HBOT in DFI.[77]

Evidence statement. There is no evidence of high quality that hyperbaric oxygen treatment improves any infection related outcomes of diabetic foot ulcers.

Quality of evidence. Low.

References. Doctor et al[77]

4 | DISCUSSION

This updated systematic review was designed to include all studies in any language published before July 2018 of treatments of DFI in which an intervention group was compared with a concurrent control group. In this report, we have grouped the included studies by the PICOs we developed for assessing this topic. The largest group of studies was those related to antibiotic treatments for SSTI and osteomyelitis. To some extent, the separation of these two groups is debatable, as the various studies used different definitions for osteomyelitis (and SSTI), the percentage of subjects with osteomyelitis was sometimes small, and infected bone was removed prior to inclusion in most trials. This may explain the apparent resolution of a substantial number of included cases labelled as having osteomyelitis with only a relatively short course of antibiotic therapy. In addition to short-term measures of microbiological response and apparent clinical cure, studies of the treatment of osteomyelitis should optimally include some measures (clinical, laboratory, and imaging) of long-term clinical remission.

We identified a total of 53 articles that met our inclusion criteria, 13 of which were published in the 4 years since our last systematic review of this subject. The quality of trial design has generally been higher 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 DFO, and evidence continues to emerge to justify the non-surgical (antibiotic) management of many cases of osteomyelitis, but progress in other treatment related areas is limited. Thus, the antibiotic choice for most DFIs largely remains a matter of expert opinion and local circumstances, as do the criteria used to determine route and duration of antibiotic treatment for both osteomyelitis and infections of skin and soft tissue alone. Although we found no studies in DFI to directly support the common practice of adjusting empiric treatment to local prevalence and antimicrobial resistance profiles, we believe considering these factors important in selecting an appropriate empiric antimicrobial regimen.

The available literature on antimicrobial therapy for DFI provides no robust data to specifically support or discourage the treatment with oral (vs parenteral) antimicrobial therapy. We are aware of only one RCT comparing intravenous versus predominantly oral antimicrobial therapy for soft tissue or bone infections, which showed similar results for the two routes of therapy,[62] Unfortunately, in this study, the data on subjects with DFO were not separately analysed. Although the RCT therefore did not qualify to be included in the systematic review, we decided to include the reference in the evidence statement. The quality of evidence of the statement remained "low". Given the generally accepted rules for antimicrobial stewardship, and the absence of evidence of superiority of any antibiotic in treatment of DFI, we advocate to prescribe antibiotics with the narrowest possible spectrum for as short a duration as possible and by the oral route, if possible.

There are no studies that directly compare different durations of treatment for skin and soft tissue DFIs, but based on data from clinical in trials of different antibiotics, 10 to14 days appears to be sufficient. It is unclear what factors to consider when deciding to shorten or prolong antimicrobial treatment in individuals with skin and soft tissue DFI. It is especially uncertain if the presence of peripheral artery disease requires prolonging prolongs the duration of antimicrobial treatment.

The required duration of treatment for patients with osteomyelitis seems to be no more than 6 weeks. This is based on several published the trials that compared outcomes of two antimicrobials in DFO, where most subjects underwent some form of bone debridement, and one trial in subjects with forefoot DFO, that did not require immediate surgery, whom were treated for 6 or 12 weeks. It remains uncertain whether some patients would do well with a shorter duration or if some (eg, those with exposed bone, hindfoot osteomyelitis, incomplete infected bone resection, and peripheral artery disease) need a longer duration of treatment with antibiotics. Also, we found no studies that specifically investigated the importance of treating with antimicrobials with anti-biofilm properties (eg, rifampi[ci]n). Use of a regimen including rifampi(ci)n in prosthetic joint associated infections seems to lead to better outcomes that regimens without rifampi(ci)n.

Although topical antimicrobial therapy has some theoretical benefits, and some agent antimicrobials seem promising in case reports, there are no high-quality studies to support the use of topical antimicrobials for DFIs. Similarly, there is no strong evidence to support the use any of several various adjunctive therapies as new topical antimicrobials (eg, polypeptides), new vehicles to deliver topical antibiotics (eg, sponges), and new devices are constantly being developed, this conclusion might change in the future.

4.1 | Limitations

The main limitation of this systematic review is that our literature search failed to identify five studies that should have been included, which we later found by cross-referencing the literature. This may have resulted from our search criteria being too narrowly focused, leading to a lower sensitivity. Another limitation is that we only included studies of high quality that enrolled sufficient numbers of subjects with diabetes mellitus. We do not think, however, that we have excluded articles that might have changed the outcomes of the PICOs with this strategy. Another limitation is that we failed to record the reasons for excluding studies during our review of the literature. Furthermore, the operational definitions of diagnosis and outcome, including those for diagnosis of osteomyelitis and SSTI, varied among the identified studies. In particular, some of the studies included an unknown percentage of subjects with osteomyelitis, unclear methods for identifying method to identify the type and number of pathogens, unknown levels of antimicrobial resistance, unclear types of surgical procedures, unknown types of antimicrobial agents used for treatment, and variable definitions of microbiological and clinical cure. We think it is vitally important for future research that researchers strictly adhere to agreed definitions of diagnosis and treatment to enable comparison of outcomes of studies.[78]

4.2 | Suggestions for future research

Knowledge gaps in literature are as follows:

1. What is the optimal duration of treatment for skin and soft tissue DFI?
2. What is the optimal duration of antibiotic therapy for DFO treated without surgery?
3. What is the optimal duration of antimicrobial treatment for DFO treated with bone resection surgery?
4. What is the influence of the presence of peripheral artery disease on outcomes of treatment of DFI, and specifically on the appropriate on duration of antimicrobial therapy?
5. Is complete oral antibiotic therapy as effective as parenteral treatment for DFI, including DFO?
6. Does an antibiotic regimen that includes rifampi(ci)n leads to higher cure rates in staphylococcal DFO?

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CONFLICT OF INTEREST

Full conflict of interest statements of all authors can be found online at www.iwgdfguidelines.org.

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AUTHOR CONTRIBUTIONS

E.S., E.J.P., S.A.V., and B.A.L. participated in the writing of the document, and all the working group members participated in the literature search, the evaluation of the content and quality of the articles selected for the analysis, and review of the final document.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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