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REVIEW ARTICLE

Interventions in the management of diabetes-related foot infections: 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 from 30 June 2018 to 30 June 2022. We

Abbreviations: CRP, C-reactive protein; DFI, diabetes-related foot infection; DFO, diabetes-related osteomyelitis of the foot; DFU, diabetes-related foot ulcer; ESR, erythrocyte sedimentation rate; IDSA, Infectious Diseases Society of America; IWGDF, International Working Group on the Diabetic Foot; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PCT, procalcitonin; PET, positron emission tomodensitometry; PICO, population intervention control outcome; SR, systematic review; ST-DFI, soft-tissue diabetes-related foot infection; STI, soft-tissue infection.

combined this search with our previous literature search of a systematic review performed in 2020, in which the infection committee of the International Working Group on the Diabetic Foot searched the literature until June 2018. We defined the context of the literature by formulating clinical questions of interest, then developing structured clinical questions (Patients-Intervention-Control-Outcomes) 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 methodological quality. Our literature search identified a total of 5,418 articles, of which we selected 32 for full-text review. Overall, the newly available studies we identified since 2018 do not significantly modify the body of the 2020 statements for the interventions in the management of diabetes-related foot infections. The recent data confirm that outcomes in patients treated with the different antibiotic regimens for both skin and soft tissue infection and osteomyelitis of the diabetes-related foot are broadly equivalent across studies, with a few exceptions (tigecycline not non-inferior to ertapenem [±vancomycin]). The newly available data suggest that antibiotic therapy following surgical debridement for moderate or severe infections could be reduced to 10 days and to 3 weeks for osteomyelitis following surgical debridement of bone. Similar outcomes were 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 recent adjunctive therapies, such as cold plasma for infected foot ulcers and bioactive glass for osteomyelitis. Our updated systematic review confirms a trend to a better quality of the most recent trials and the need for further well-designed trials to produce higher quality evidence to underpin our recommendations.

KEYWORDS
diabetes mellitus, diabetic foot, foot ulcer, infection, osteomyelitis, systematic review

1 | INTRODUCTION

Diabetes-related foot infections (DFIs) are associated with considerable morbidity, a worsened quality of life, and a marked increase in the risk of lower extremity amputation.[1,2] Because appropriate treatment will very likely improve the outcome of these infections, we have reviewed the available evidence to help establish evidence-based criteria for selecting treatment. 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 the treatment of DFI conducted in 2019 and published in 2020.[3] 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. This review does not focus on definitions of infection or on methods for diagnosis; for our review on the accuracy of diagnostic procedures in DFIs, we refer to our parallel publication on this topic.[4]

2 | METHODS

We performed the literature search for this systematic review for the period from 30 June 2018 to 30 June 2022 on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5] On 10 May 2022, we prospectively registered the systematic review in the PROSPERO 2022 database for systematic reviews, which assigned it the number CRD42022324812 (https://www.crd.york.ac.uk/PROSPEROFILES/324795_STRATEGY_20220426.pdf).

We began by defining the population (patients) of interest (P), interventions (I) performedand outcomes (O) assessed that we would attempt to address. The IWGDF editorial board and 10 external experts (not members of the infection working group) from various geographical regions worldwide then reviewed these questions and population intervention control outcomes (PICOs) for their clinical relevance. Using their input, we revised the PICOs to their final form for this review. Some PICOs from the 2019 systematic review only

underwent small textural changes to improve clarity. One PICO was split into two different PICOs for readability and clarity. These changes did not have consequences for the identified publications before the 2019 search. With our oversight, a medical librarian performed electronic database searches using the databases of MEDLINE (PubMed), EMBASE, and Scopus, using a combination of MeSH and keyword terms.

We included studies on 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. We reviewed any study of an intervention (e.g. antibiotic, antiseptic, surgery and adjunctive therapy) to prevent or cure the infection in a person with a diabetes-related complication of the foot after our previous literature search. 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. We only included outcomes that were relevant to an infectious aspect of the foot. These could include clinical cure of infection, requirement for lower extremity amputation, occurrence of a new infection, death, hospitalisation, resolution of a foot ulcer, eradication of microbial pathogens, quality of life, adverse effects, or cost of treatment. The infection working group agreed that acceptable study designs could include meta-analyses, systematic reviews, randomized controlled trials (RCTs), non-randomised comparative studies, case-control studies, and prospective and retrospective cohort studies. We excluded papers that were conducted on non-human subjects, review articles, case series without a contemporaneous control group, studies in which the reported data on the evaluation of the diabetic population was not individualised, and studies that included fewer than 15 patients with diabetes. We used the same search string as the one we employed in 2018 with the addition of new terms in relation to new antibiotics and other therapeutic interventions.[3] The search criteria were only augmented with specific antimicrobials and techniques that became available after 2018. The search string was designed to identify all prospective and retrospective studies, in any language, that evaluated interventions for the treatment of DFIs in the given population and that were published after our previous search, that is, between 30 June 2018 and 30 June 2022. We also searched the ClinicalTrials.gov (https://clinicaltrials.gov) and the World Health Organization-International Clinical Trials Registry Platform 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. To test the search terms we intended to employ, we first created a set of 20 key publications that we knew should be in the scope of the systematic review that had to be identified in the literature search. Our search terms identified all 20 publications.

After conducting the literature search, we divided the papers retrieved and assigned one-sixth of the papers to one of six infection working group teams of two members each. These working group members, working independently, reviewed their assigned publications by title and abstract to determine eligibility on the basis of the presence of the criteria listed above (appropriate population, study design, outcome(s) measurement, and intervention(s)), using the COVIDENCE online software (https://app.covidence.org). After the two members of each team reached a consensus on which papers met the criteria, they obtained and independently reviewed the full paper of all potentially eligible publications using the same key criteria to determine final eligibility for inclusion.[6] Any disagreements between assessors were discussed until a consensus was reached, with a third assessor being involved if needed. All included full-text publications were assessed for risk of bias with forms of the Dutch Cochrane Centre by two independent assessors. The SIGN level of evidence was determined for each publication (https://www.sign.ac.uk/assets/study_design.pdf) and combined with the risk of bias score.[7] Depending on the number of questions answered with 'yes' on the 10 items of the Cochrane scoring sheet, risk of bias for each study was very low when scoring ≥8/10, low when scoring 6–7/10 or high when scoring ≤5/10. After appropriate data were extracted from each included paper, they were summarised in a standardised evidence table that included study design, risk of bias, setting, follow-up, study population and characteristics, the variable or condition assessed, the study intervention and the control intervention, results of analyses, and an open field for comments. Through both electronic communications and an in-person meeting, each member of the working group reviewed and discussed the content of the evidence tables. Working group member(s) did not participate in the selection or the discussion of a paper if they were (co)-authors of that paper.

In the Results Section, risk of bias assessment and evidence tables are shown of studies found in the updated search. For those details on earlier studies, we refer to our previous systematic review.[6] In the description of the results and in the evidence statements, we used the information from studies identified in both the previous and this updated search.

2.1 | Evidence statements

Based on the strength of the available evidence, we formulated evidence statements with the accompanying assessment of the quality of the evidence, according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology.[8] The authors rated the certainty of the evidence for each formulated evidence statement as 'high', 'moderate', 'low', or 'very low' in regard to the strength of confidence in estimates of the effect an intervention on patient-important outcomes. GRADE defines 'high' as 'We are very confident that the true effect lies close to that of the estimate of the effect'; 'moderate' as 'We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different';

'low' as 'Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect', and 'very low' as 'We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect'. The rating was determined based on the level of evidence, risk of bias, (in)consistency of results, (im)precision, (in) directness, publication bias, effect size and evidence of dose-response relation. Each evidence statement was phrased in accordance with the methods described by GRADE. All authors discussed these evidence statements until consensus was reached. After each evidence statement, the related literature is discussed.

3 | RESULTS

The PRISMA flowchart with the study selection process is shown in Figure 1. The risk of bias assessment of each paper can be found in Table 1. The full evidence table of the papers published after the 2019 search can be found in Appendix S1.

We report on the following topics:

- PICO 1: choice (1.1) and duration (1.2) of antimicrobial therapy in soft tissue foot infection,
- PICO 2: choice of antimicrobial therapy in diabetes-related osteomyelitis of the foot (DFO) (2.1) and the duration of conservative treatment (2.2) or after surgical bone resection (2.3),
- PICO 3: early surgery (3.1) and primary surgery or non-surgical therapy for DFO (3.2),
- PICO 4: additional therapies: local antibiotics and antiseptics (4.1), acidifying agents for Pseudomonas (4.2), rifampicin for DFO (4.3), negative wound pressure therapy (4.4), bioactive glass for DFO (4.5) and cold atmospheric plasma (4.6).

3.1 | PICO 1

In a person with diabetes and a soft tissue infection of the foot, is any particular antibiotic regimen (specific agent[s], route of administration, duration) better than any other regarding the resolution of infection, recurrence of infection, and the acquisition of antimicrobial resistance?

3.1.1 | Choice antibiotic therapy for ST-DFIs

Summary of the literature

A recent systematic review[30] reached the same conclusions as our 2019 systematic review[3] regarding the absence of any strong evidence to recommend a specific antibiotic with the highest efficacy. With some exceptions,[41–43] many of the previously described studies on soft-tissue infection (STI) in the foot of persons with diabetes were characterised by suboptimal trial design and reporting. Only two studies did report a difference in outcome between the two tested antibiotics. One was a study that suggested the inferiority of tigecycline to ertapenem with or without vancomycin soft-tissue diabetes-related foot infections (ST-DFIs)[42] and the other a study that suggested the inferiority of ertapenem to piperacillin-tazobactam in a subset of persons with a severe ST-DFIs.[43]

One high-quality study compared the results of therapy with tigecycline (alone) and ertapenem (with or without the addition of vancomycin) in hospitalised subjects with an acute DFI of any severity.[42] The study assessed individuals with diabetic foot infection without osteomyelitis (primary study) and with osteomyelitis (sub study). The tigecycline regimen did not meet the primary study endpoint of non-inferiority to the ertapenem ± vancomycin regimen. The percentage of adverse events (primarily nausea and insomnia) was significantly higher in the tigecycline-treated group. The other high-quality study was a non-inferiority, multi-centre trial of ertapenem versus piperacillin/tazobactam (with or without the addition of vancomycin in either group) in subjects with moderate or severe soft tissue DFIs without osteomyelitis.[43] The outcomes suggest that ertapenem was clinically non-inferior to piperacillin/tazobactam in patients with moderate or severe DFIs. In a subset analysis, subjects with a severe DFI treated with ertapenem had a significantly lower clinical resolution rate, compared with subjects treated with piperacillin/tazobactam (91.5% vs. 97.2% [119/130 vs. 139/143], $p = 0.04$). Because the study was not powered to detect statistical differences between study treatments in the severe DFI stratum, it is hard to draw solid conclusions from this observation. 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 found no statistically significant differences in outcomes between the treatment arms.[43,44]

Following our 2019 review, we identified 3 additional, recent papers that compared the efficacy of different systemic antibiotics for the treatment of ST-DFIs.[14,21,33] In a series of 794 initial episodes of DFIs in 419 patients, including 339 episodes of DFO, all patients were treated with surgical debridement.[14] Beta-lactam antibiotics were used in 631 episodes (79%) including oral amoxicillin-clavulanate at a daily dose ranging from 2 to 3 g for a median of 20 days (interquartile range, 12–30 days) in 301 episodes. After a median follow-up of 3.3 years, amoxicillin-clavulanate and non-beta-lactam antibiotics (mostly fluoroquinolones, vancomycin, and clindamycin) resulted in comparable remission (respectively 74% and 79%: $p = 0.15$). A total of 61 methicillin-resistant *Staphylococcus* spp. were identified, which presumably were treated with non-beta-lactam antibiotics. The routine use of amoxicillin-clavulanate in patients treated for DFIs is, however, limited by the increasing prevalence of methicillin-resistant staphylococci and resistant gram-negative rods in many countries in the world. Importantly, these data do not apply to patients treated medically (i.e., without any surgical intervention) for DFI or DFO. A small randomised-controlled trial with high risks of bias compared linezolid (600 mg bid) and ampicillin-sulbactam (1.5–3 g q6h iv), and oral amoxicillin-clavulanate

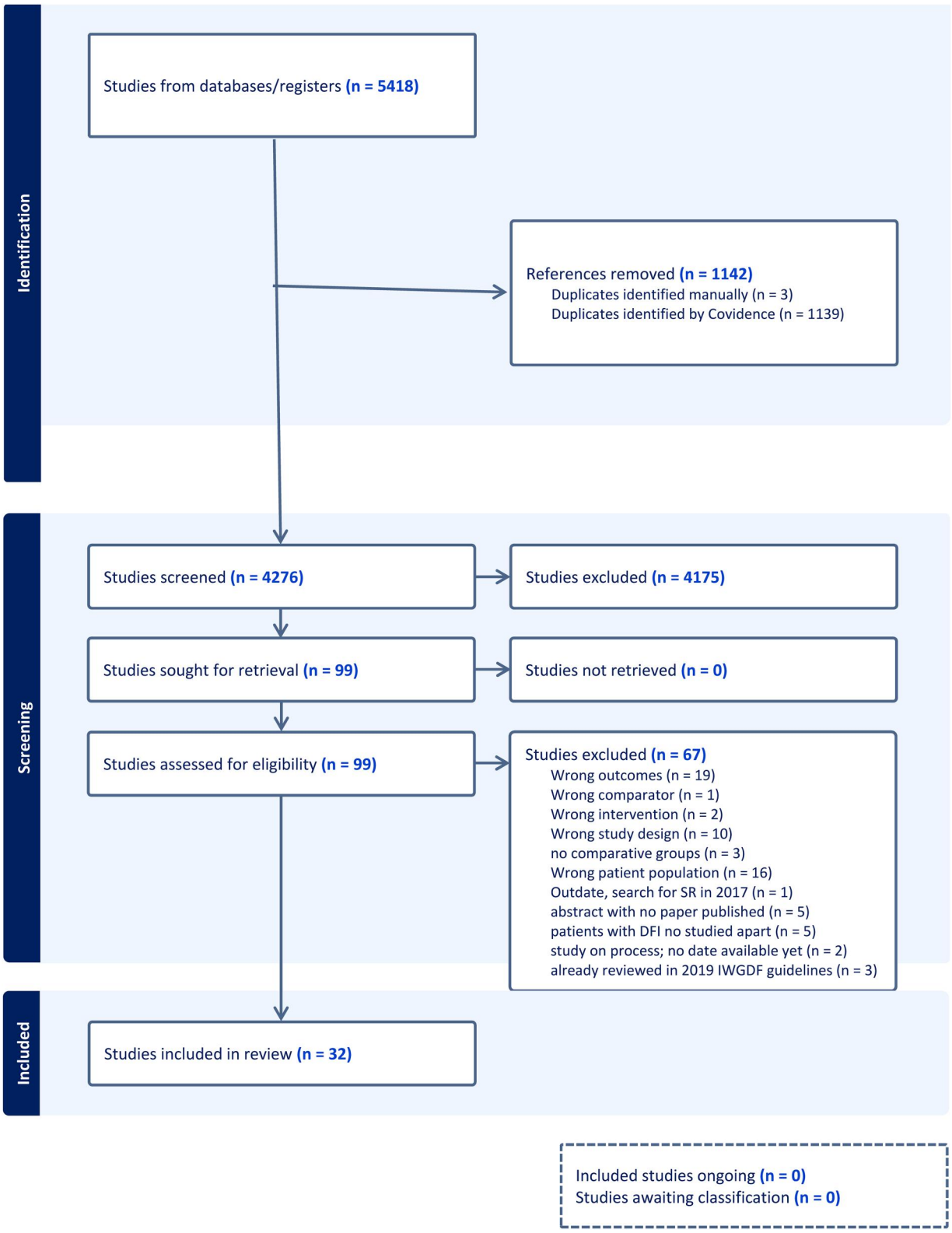

FIGURE 1 Flow diagram for 2023 systematic review on the intervention for diabetes-related foot infections.

(500–875 mg every 8–12 h) as empirical treatment of infected diabetic foot ulcers.[21] The duration of treatment ranged from 7 to 28 days. Ulcer healing was recorded in 17/25 (68%) patients in the linezolid group and in 14/25 (56%) other patients ($p = 0.76$). In this study, no microbiology results were provided, which makes the interpretation of the results difficult.

The use of carbapenem antibiotics is usually necessary for the treatment of multiresistant DFIs.[3,45] In a multicenter observational

TABLE 1 Risk of bias assessment of 32 included studies in the 2023 systematic review.

Studies (refs)	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Certainty of evidence
Brodell (2021)[9]						Low
De Giglio (2021)[10]						Low
Fejfarova (2019)[11]						Low
Feldman (2021)[12]						Low
Gariani (2019)[13]						Low
Gariani (2019)[14]						Moderate
Gariani (2021)[15]						Moderate
Gill (2022)[16]						Low
Haug (2022)[17]						Low
Iranparvar (2019)[18]						Low
Jaber (2022)[19]						Low
Kastrin (2021)[20]						Low
Kaur (2021)[21]						Low
Kim (2022)[22]						Low
Lavery (2020)[23]						Moderate
Lin (2021)[24]						Moderate
Marson (2018)[25]						Low
Memon (2022)[26]						Low
Mendame Ehya (2021)[27]						Low
Pham (2021)[28]						Low
Pham (2022)[29]						Moderate
Pratama (2022)[30]						Moderate
Qin (2019)[31]						Low
Rossel (2019)[32]						Low
Saltoglu (2021)[33]						Moderate
Sergeev (2020)[34]						Low
Sipahi (2021)[35]						Low
Stratmann (2020)[36]						Low
Tardáguila-García (2021)[37]						Moderate
Tardáguila-García (2021)[38]						Low
Wilson (2019)[39]						Low
Zhou (2021)[40]						Low

Note: Green box: not serious risk of bias; red box: serious risk of bias.

prospective study from Turkey, which included 284 patients hospitalised for a moderate or severe DFI, a multivariate analysis was performed to identify the risk factors of reinfection, major amputation, and death during a 6-month follow-up.[33] A major amputation was necessary in 12.7% of the population. Four independent risk factors for major amputation were identified, including vascular insufficiency (p = 0.004), hospital readmission (p = 0.009), C-reactive protein (CRP) >130 mg/L (p = 0.007), and carbapenems use (p = 0.005). However, there are doubts about the statistical analyses performed in this study. In the multivariate models, there was inadequate adjustment for the severity of the infection and carbapenems might have been used in more severe or non-responding cases. This limitation makes it difficult to draw reliable conclusions.[33] We added 'acquisition of antimicrobial resistance' in the 2023 PICO, a term that was not included in the 2019 PICO. We did not find outcome data for antimicrobial resistance in the extracted data of the papers identified in the 2019 systematic review.

Evidence statement

There were no differences in all potential clinical outcomes among antibiotics compared in studies of soft-tissue-DFIs (except in a study advocating the tigecycline inferiority to ertapenem with or without vancomycin).

Certainty of evidence

Moderate, based on numerous studies including recent RCTs and older randomised and non-randomised studies.

References 2018–2022

Gariani 2019,[14] Kaur 2021,[21] Saltoglu 2021,[33] Pratama 2022.[30]

References prior to 2018

Bradsher, 1984; Lipsky, 1990; Siami, 2001; Graham, 2002; Xu, 2016; Graham, 2002; Clay, 2004; Lobmann, 2004; Harkless, 2005; Lipsky, 2005; Noel, 2008; Vick-Fragoso, 2009; Schaper, 2013; Lauf, 2014; Saltoglu, 2010; Lipsky, 2005; Lauf, 2014; Grayson, 1994; Erstad, 1997; Lipsky, 1997; Lipsky, 2004; Lipsky, 2007.[41–44,46–62]

3.1.2 | Duration antibiotic therapy for ST-DFIs

Summary of the literature

The evidence statement of the 2020 systematic review[3] suggested that soft-tissue DFI need not be treated for longer than 2 weeks.[41–44,46–65] Two more recent single-centre retrospective studies[13,17] did not show any link between antibiotic duration and microbiological failure or clinical recurrences of DFI. The first one collated 1018 moderate or severe DFI episodes (392 episodes of DFO including those with residual bone infection after amputation), of which 313 cases involved revascularisation.[13] Surgical debridement and amputation were performed in respectively 824 episodes (81%), and 596 (59%) cases. The median total duration of antibiotic therapy was 20 days and the median follow-up was 3 years. On multivariate analysis, the duration of antibiotic therapy did not affect the risk of recurrence (HR 1.0, 95% CI 0.99–1.01). Stratifying the analysis according to the type of DFI (ST vs. DFO) did not modify the results. The second single-centre retrospective study included for a 20-year period (2000–2020) 721 episodes of DFI treated with systemic antibiotics and surgery.[17] [Correction added on 9-November-2023, after first online publication, 'from the same group' has been removed from the sentence.] As in the other study, clinical failure was not associated with the total duration of antibiotic therapy. Both studies could not determine a threshold for the optimal duration of antibiotic therapy to prevent recurrences of DFI and clinical failures. It remained unclear how participants were recruited and how many of them were included in both studies.

In a prospective randomised-controlled trial, involving patients with moderate or severe ST-DFIs treated with surgical debridement, 35 received 10 days of antibiotic therapy, and 31 other patients, 20 days. This pilot study reported preliminary data from a larger RCT that is underway. Similar rates of cure and antibiotic-related adverse events were recorded in both groups.[29] Limitations of this study were that it was underpowered, that it had a large non-inferiority margin of 25%, and that the proportion of participants with a moderate versus those with a severe ST-DFIs was not reported. In all studies investigating the duration of total antibiotic therapy, 'time zero' always started with the (intraoperative) debridement. So far, the influence of presurgical antibiotic duration on the ultimate outcomes after surgery has not been evaluated. The limited data from the pilot study suggested that antibiotic therapy for DFIs following surgical debridement for 20 and 10 days leads to comparable outcomes.[29] Reduction of the duration of antibiotic treatment from 14, as recommended in 2019, to 10 days in surgically treated patients could therefore provide an opportunity to reduce the exposure of patients to potential antibiotic-related adverse effects.

Evidence statement

No conclusive data could be identified to determine the optimal duration of systemic antibiotic therapy in relation with the outcome of soft-tissue DFIs, while limited data advocate that a 10-day duration may be enough for moderate or severe DFIs treated with surgical debridement.

Certainty of evidence

Low, based on retrospective studies and one small recent RCT with a risk of bias.

References 2018–2022

Gariani 2019,[13] Haug 2022,[17] Pham 2022.[29]

References prior to 2018

Bradsher, 1984; Lipsky, 1990; Siami, 2001; Graham, 2002; Xu, 2016; Graham, 2002; Clay, 2004; Lobmann, 2004; Harkless, 2005; Lipsky, 2005; Noel, 2008; Vick-Fragoso, 2009; Schaper, 2013; Lauf, 2014; Saltoglu, 2010; Lipsky, 2005; Lauf, 2014; Grayson, 1994; Erstad, 1997; Lipsky, 1997; Lipsky, 2004; Lipsky, 2007; Lázaro-Martínez, 2014; Ulcay, 2014; Tone, 2015.[41–44,46–65]

3.2 | PICO 2

In a person with diabetes and a bone and/or joint infection of the foot, is any particular antibiotic regimen (specific agent[s], route of administration, total and parenteral duration) better than any other regarding the resolution and recurrence of infection.

3.2.1 | Choice of antibiotic treatment for DFO

Summary of evidence

In the 2019 systematic review, we identified 13 studies conducted in patients with diabetic foot osteomyelitis.[42,44,46–51,63–67] Seven of these RCTs compared the use of a beta-lactam/beta-lactamase inhibitor combination antibiotic in DFO against one of the following agents: imipenem/cilastatin[46,47]; cefoxitin[48]; ofloxacin[49]; linezolid[50];

ertapenem[44]; or moxifloxacin.[51] Results of each of these studies reported no significant differences in outcomes among the different antibiotic regimens with the exception of two studies.[42,48] The first of these was a sub study of 118 participants with osteomyelitis in the large RCT reported a higher cure rate patients treated with ertapenem ± vancomycin compared with those treated with of tigecycline (discussed above in the skin and soft tissue infection section).[42] In the other single centre, double-blind study, 36 subjects were treated with either cefoxitin or ampicillin/sulbactam.[48] Subjects in the cefoxitin group had a significantly higher rate of 'cure' than subjects in the ampicillin/sulbactam group, but outcome 'cure or improvement' was not statistically different.

The quality of most, but not all (see Appendix S1), of these studies was generally high. In one non-inferiority RCT, randomised 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.[68,69] 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.

We identified four new studies[15,16,18,33] since the systematic review of 2020,[3] and another systematic review mentioned earlier.[30] Whether oral antibiotic therapy is superior to intravenous antibiotic therapy for residual osteomyelitis following amputation for DFIs was addressed in two recent studies.[14,16] A retrospective study included a total of 65 evaluable patients without providing data on a power calculation of the necessary population size.[16] Failure was defined as the need for a revision surgery (including debridement and irrigation or proximal amputation), and/or a persistent nonhealing wound with draining sinus tract at the surgical site within 12 months after the initial amputation or remission. Thirty patients were treated intravenously and 35 orally. Failure was recorded in 32 (49%) patients, with 17 (53%) in the oral group and 15 (47%) in the intravenous group. No statistically significant difference was found between the two groups of patients according to the mode of antibiotics administration (proportional difference: −14%, 95% CI: −36% to 10%). In another single-centre retrospective cohort study, a series of 794 DFI episodes, including 339 DFO cases, compared the efficacy of oral amoxicillin-clavulanate to that of other antibiotic regimens administered either orally or intravenously.[14] Oral amoxicillin-clavulanate was prescribed for a median of 20 days (interquartile range, 12–30 days, 30 days for DFO). After a median follow-up of 3.3 years, 178 DFIs (22%) overall recurred (DFOs, 75; 22%). Remission was recorded in 74% of the cases treated with oral amoxicillin-clavulanate compared with 79% with other regimens ($p = 0.15$). In the multivariate and stratified subgroup analyses, oral amoxicillin-clavulanate resulted in similar clinical outcomes to other antimicrobial regimens, when used orally from the start, after initial parenteral therapy, or when prescribed for DFO.

An RCT compared the efficacy of 6-week versus 12-week antibiotic therapy in the nonsurgical treatment of diabetic foot osteomyelitis.[18] DFO was diagnosed on a combination of a positive probe-to-bone probe test with abnormalities on radiography compatible with bone involvement, and elevated laboratory tests including leucocytosis and erythrocyte sedimentation rate. Patients were randomly assigned to a 6-week clindamycin or 12-week ciprofloxacin regimen. No significant difference in clinical outcomes between the two groups was recorded (11 complete improvements out of 15 in both groups) at the end of a 3-month post-end of treatment follow-up. The conclusions of the study are limited by the small number of patients (30), the use of different antibiotic regimens in the two groups of patients, a short follow-up period, and the lack of information about bone microbiology.

The study by Saltoglu and co-workers mentioned earlier, also included patients with DFO. The smaller number of this subgroup limits the possibility to draw reliable conclusions in patients with DFO.[33]

Evidence statement

There were no differences in all potential clinical outcomes among antibiotics compared in studies of DFO (except in a study advocating the tigecycline inferiority to ertapenem with or without vancomycin).

Certainty of evidence

Moderate, based on numerous studies including RCTs and older randomised and non-randomised studies.

References 2018–2022

Pratama 2022,[30] Gariani 2019,[14] Saltoglu 2021.[33]

References prior to 2018

Senneville, 2008; Tone, 2015; Lesens, 2015; Lázaro-Martínez, 2014; Ulcay, 2014; Saltoglu, 2010; Lipsky, 2005; Grayson, 1994; Erstad, 1997; Lipsky, 1997; Lipsky, 2004; Lipsky, 2007.[42,44,46–51,63–67]

3.2.2 | Duration antibiotic therapy for DFOs treated conservatively

Summary of the literature

In the 2020 systematic review, the most important study covering this topic was an RCT that compared 6 weeks versus 12 weeks of antibiotics for patients with a DFO treated with antibiotics, but not with surgery.[3,65] In this study, the outcomes were comparable between the two treatment arms.[65] In the literature search that encompassed studies published between 2018 and 2022, we identified two additional studies. One was a retrospective multicentre study from Turkey in which the cyclic lipopeptide antibiotic daptomycin and the glycopeptide antibiotic teicoplanin were compared and that included 16 patients (8 in each group) diagnosed with DFO on the basis of imaging and/or bone biopsy results.[35] Remission based on the resolution of clinical signs of infection assessed at the end of the antibiotic therapy (primary outcome) and 1 month later (secondary outcome) was recorded in both groups in 7 (87.5%) in both

groups. The daily dose of daptomycin was 500 mg and ranged from 400 to 800 mg for teicoplanin. Daptomycin and teicoplanin were administered for a mean duration of respectively, 35.1 ± 22.7 and 45.2 ± 27.4 days. The main limitations of this study concern (i) the definition of remission of DFO limited to clinical signs of infection, (ii) the very short follow-up duration, (iii) the small number of patients and (iv) the absence of data regarding the use of a concomitant antibiotic during treatment.

An RCT mentioned earlier compared the efficacy of 6-week versus 12-week antibiotic therapy in the nonsurgical treatment of diabetic foot osteomyelitis with different antibiotics.[18] No significant difference in clinical outcomes between the two groups was recorded. The conclusions of the study are limited by the small number of patients ($n = 30$), the use of different antibiotic regimens in the two groups of patients, a short follow-up period, and the lack of information about bone microbiology. This study had the same conclusions as a previous RCT on the same topic.[65]

Evidence statement

A 6-week duration of systemic antibiotic therapy seems appropriate for DFOs treated medically.

Certainty of evidence

Moderate, based on one recent RCT and one recent retrospective, combined with older (non-randomised) studies, all with a high risk of bias.

References 2018–2022

Iranpavar 2019,[18] Sipahi 2021.[35]

References prior to 2018

Bradsher, 1984; Lipsky, 1990; Siami, 2001; Graham, 2002; Xu, 2016; Graham, 2002; Clay, 2004; Lobmann, 2004; Harkless, 2005; Lipsky, 2005; Noel, 2008; Vick-Fragoso, 2009; Schaper, 2013; Lauf, 2014; Saltoglu, 2010; Lipsky, 2005; Lauf, 2014; Grayson, 1994; Erstad, 1997; Lipsky, 1997; Lipsky, 2004; Lipsky, 2007; Lázaro-Martínez, 2014; Ulcay, 2014; Tone, 2015.[41–44,46–65]

3.2.3 | Duration of antibiotic therapy for DFO after resection of bone

Summary of the literature

Compared with our 2020 review, there were more recent studies that specifically evaluated the duration of antibiotic treatment in combination with surgical debridement of infected bone tissue in patients with a DFO. We identified two studies that addressed the duration of systemic antibiotic therapy for DFO treated surgically.[15,32] Gariani et al. compared 3 weeks versus 6 weeks of systemic antibiotic treatment in a prospective, randomised, non-inferiority, pilot trial.[15] A total of 93 patients (18% females; median age 65 years) were enroled, including 44 in the 3-week arm and 49 in the 6-week arm. The median number of surgical debridements was 1 (range, 0–2 interventions). After a minimal duration of follow-up of 2 months, remission was recorded in 37/44 (84%) and 36/49 (73%) patients in the 3- and 6-weeks arm, respectively ($p = 0.21$) in the intention-to-treat (ITT) population and 33/39 (84.6%) versus 32/43 (74.4%); $p = 0.26$ in the per-protocol (PP) population. The number of adverse events attributable to the antibiotic treatments was similar in the two study arms. The shorter antibiotic course was not significantly associated with remission (for the ITT population, hazard ratio 1.1, 95% CI 0.6–1.7; for the PP population hazard ratio 0.8, 95% CI 0.5–1.4) in the multivariate analysis. Importantly, the conclusions of this study do not apply to patients treated conservatively (i.e., with antibiotics but without surgery) for DFO. One retrospective study aimed at answering to a commonly debated question relating to the appropriate duration of antibiotic therapy for DFIs including DFO after amputation.[32] A total of 482 DFI episodes including 239 (50%) DFOs were included. The median duration of systemic antibiotic administration was 7 days (IQR, 1–16 days) and the median duration of parenteral use was 5 days (IQR, 0–12 days). The entire antibiotic course was intravenous in 97 (20%) cases and oral in 69 cases (including perioperatively) and antibiotics were discontinued immediately after the intervention in 109 cases (25%). Clinical failure at the same anatomical site occurred in 90 cases (17%) within 1 year, including 38 due to the same microorganism. The Cox regression analysis showed that neither the total duration of post-amputation antibiotic therapy nor the immediate postoperative discontinuation of antimicrobials after surgery influenced the failure rate. The authors found no benefit in continuing postsurgical antibiotic administration in routine amputation for DFI. Of note, the study does not differentiate which surgeries were for STIs and/or DFOs, which prevents from assessing whether failures were related to residual DFO or not. CRP monitoring does not seem to be of any help in determining the outcomes of the infection and thus the optimal duration of the antibiotic treatment of DFI including DFO.[28]

Evidence statement

A 3-week period of systemic antibiotic therapy seems appropriate for DFO treated with surgical debridement of infected bone tissues; duration and mode of administration (oral vs. intravenous) of the antibiotic therapy following amputation for a DFI with or without residual DFO does not seem to influence the outcome.

Certainty of evidence

Low, on the basis of one recent RCT and 4 recent retrospective studies, and older (non-randomised) studies, all with substantial risks of bias.

References 2018–2022

Gariani 2019,[15] Rossel 2019,[32] Pham 2021,[28] Gariani 2021,[14] Gill 2022.[16]

References prior to 2018

Bradsher, 1984; Lipsky, 1990; Siami, 2001; Graham, 2002; Xu, 2016; Graham, 2002; Clay, 2004; Lobmann, 2004; Harkless, 2005; Lipsky, 2005; Noel, 2008; Vick-Fragoso, 2009; Schaper, 2013; Lauf,

2014; Saltoglu, 2010; Lipsky, 2005; Lauf, 2014; Grayson, 1994; Erstad, 1997; Lipsky, 1997; Lipsky, 2004; Lipsky, 2007; Lázaro-Martínez, 2014; Ulcay, 2014; Tone, 2015.[41–44,46–65]

3.3 | PICO 3

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)?

3.3.1 | Early surgery in severe DFIs with and without DFOs

Summary of the literature

Our previous systematic review[3] identified two low-quality studies that suggested that early surgical debridement reduced the likelihood of a major amputation.[70,71] Our search identified two additional single-centre, retrospective studies that investigated the effect of treatment with 'early' surgery, including toe, foot and leg amputations (variously defined, but usually within 72 h of presentation) versus delayed surgery (i.e., 3–6 days after admission) in hospitalised patients with a severe, deep DFI, with or without osteomyelitis.[24,40] In the first study, an above knee amputation was required in 2 out of 26 patients who initially underwent conservative treatment and deferred a below the knee amputation, with a median delay of 75.5 days (23–87) after the initial recommendation to undergo a below knee amputation recommendation, and in 2 out of 18 who proceeded directly to below the knee amputation.[40] The median duration of the antibiotic therapy was significantly higher in the group of patients with deferred amputation (55 days [42–78] vs. 17 days [10–37]; $p = 0.0017$). During the follow-up of about 4 years, the hazard ratio for death was 12.2 (95% CI, 1.58–94.8) in patients in the deferred group compared with the other patients. The second study evaluated outcomes in 668 patients with moderate or severe DFI after dividing their time to specialised treatment into quartiles.[24] Patients with DFO were not clearly described or evaluated separately. The delay in referral was quite long between groups (Q1 <9 days, Q2 9–21 days, Q3 21–59 days, Q4 >59 days). Patients with the longest delays were significantly more likely to require a major amputation.

Both studies are limited by a high risk of bias, especially including a lack of randomisation of the subjects and a lack of standardised protocols for diagnosis and for surgical (or medical and antimicrobial) treatment. Although the effect of early surgical intervention seems large, the low quality of the studies considerably reduces the quality of evidence of the evidence statement.

Evidence statement

Early surgery in patients hospitalised for severe DFIs requiring surgical intervention (e.g. to drain an abscess) appears to reduce the likelihood of a major lower extremity amputation.

Certainty of evidence

Low, based on two older and two more recent, single-centre, retrospective studies.

References 2018–2022

Lin 2021,[24] Zhou 2021.[40]

References prior to 2018

Tan, 1996; Faglia, 2006.[70,71]

3.3.2 | Primary surgery or conservative therapy for DFO

Summary of the literature

The conclusion of the 2020 systematic review was that 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. This was primarily based on one RCT that did not show a difference in outcome between patients treated with surgical intervention and antibiotics, compared with those treated without surgery but with antibiotics.[63] In our current systematic review, we identified 3 additional studies that compared surgical versus non-surgical treatment of DFO.[12,22,38] In addition, we found a systematic review that also identified these studies.[37] A prospective cohort study from Spain evaluated a cohort of 116 people admitted to hospital for DFO with a 1 year follow-up.[38] The majority of subjects required surgery and antibiotics (82.8%), the others were treated with antibiotics, but without surgery. Patients with extensive soft tissue infection and critical limb ischaemia were excluded from the study. The authors did not report the proportion of wounds that healed in each group. There were no differences in the time to heal or complications in the two groups.

A retrospective cohort study from the US reported the results of 90 people with moderate and severe DFIs.[22] The study compared subjects who required surgery with bone resection and antibiotics and local debridement without bone resection and antibiotics. There was a significantly higher proportion of subjects with DFO in the surgical treatment group (79%) compared with the antibiotic treatment group (55%; $p = 0.01$). Despite this, the subjects in the surgery group were 1.8 times more likely to heal (69% vs. 38%) than those in the antibiotic treatment group. A limitation of the study was that the authors included mixed group of DFO and STI patients. In another retrospective cohort, 60 people from Israel with DFO of the toe were evaluated for at least 2 years.[12] The outcomes of subjects undergoing toe amputation for DFO were compared with those not undergoing amputation. Subjects in the non-amputation group had a significantly higher rate of re-hospitalisation for re-infection. This resulted in 33% of subjects ultimately requiring toe amputation. There was no difference in the length of hospitalisation for the index infection or leg amputations during the follow-up period between study groups. Limitations of this study were dominated by the small number of

patients, and the lack of standardisation for confusing factors such as perfusion status, type and duration of the antibiotic therapy.

Overall, compared with a previous RCT[63] that showed similar outcomes between surgical and non-surgical approaches of DFO, non-randomised studies favour better outcomes and fewer complications when surgery is performed. Given the inherent lower chance of bias of RCTs, we value the evidence of the RCT higher than the non-randomised studies and therefore we rated the certainity of evidence as moderate.

Evidence statement

Surgical and conservative (non-surgical) approaches for the treatment of DFO lead to comparable outcomes.

Certainty of evidence

Moderate, on the basis of one recent prospective cohort and two recent retrospective studies, all with risk of bias, one systematic review, and older non-randomised and one older randomised study.

References 2018–2022

Feldman 2021,[12] Kim 2022,[22] Tardáguila-García 2021,[38] Tardáguila-García 2021.[37]

References prior to 2018

Lázaro-Martínez, 2014; Lesens, 2015; Ulcay, 2014.[63,64,67]

3.4 | PICO 4

In a person with diabetes and a foot infection, does the addition of any specific adjunctive/topical treatment to systemic antibiotic therapy and surgery improve the resolution rate of infection and time to reach this resolution, recurrence of infection, need for surgical intervention including amputation and duration of the antibiotic therapy?

3.4.1 | Local antibiotics and antiseptics for DFIs

Summary of the literature

The 2020 review identified five RCTs[72–77] and one systematic review[78] on the treatment of DFI with topical antimicrobial agents. A 2017 Cochrane systematic review concluded that there was little difference in the rate of treatment-related adverse events with topical versus systemic antibiotic therapy.[78] One RCT compared the results of treatment with a topical application of the antimicrobial peptide pexiganan versus treatment with an oral antibiotic (ofloxacin).[75] The data 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)[76,77] and no further, recent, studies were identified. 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 DFI.[72–74] Pathogen eradication was high in one study in mild infections.[73] Unfortunately, this single-blinded, single-centre study was underpowered.[73] In another study, authors found non-significant differences in clinical cure, and pathogen eradication.[72] In a 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, but significantly better 2 weeks after discontinuing treatment.[74] The study was marred by a modification of the inclusion criteria (to enhance enrolment) during the study, failure to reach the recruitment target, and a high withdrawal rate, making it is difficult to interpret the reported findings. All subjects in the studies tolerated the gentamicin-collagen sponge well.

The 2020 systematic review suggested that there is low-quality evidence that treatment with topical superoxidised water can improve outcomes of diabetic foot infection.[79–81] Drawing conclusions from these studies was severely limited by their weak trial designs, incomplete reporting and possible sources of bias and we did not identify additional studies. Studies to topical treatment with chloramines, clostridial collagenase ointment or a photo-activated gel containing cationic zinc phthalocyanine derivatives, rivanol or iodophor, all revealed insufficient evidence that these therapies improve outcomes.[82–85]

Our recent search identified 5 additional studies on adjunctive treatment in DFI, including 2 RCTs, one systematic review and two retrospective studies.[9,25–27,31] One RCT of low quality compared the efficacy of systemic antibiotics (intravenous ciprofloxacin 200 mg bid) either with or without gentamicin cream for the treatment of DFIs in 140 patients (70 each group) who underwent surgical intervention for infected or necrotic tissue removal.[26] Patients with DFO, ischaemic foot, severe immune suppressions, patients already using gentamicin, alcohol or substance abusers were excluded from the study. Clinical cure was defined as the absence of clinical signs of infection, and negative culture swab 7 days after the intervention. Significantly better outcomes (reduction in inflammation, culture negativity, clinical cure rate and microbiological eradication) were recorded in the gentamicin group versus the control group (respectively, $p = 0.03$; $p = 0.001$; $p = 0.02$ and $p = 0.03$). The other RCT included a small small-size population of patients ($n = 36$) treated with or without antibiotic (vancomycin, cefoperazone, or gentamicin)-loaded bone cement for the primary treatment of diabetic neuropathic foot ulcers complicated by osteomyelitis.[27] The results of this low-quality study suggest that antibiotic-loaded bone cement versus no bone cement is associated with lower postoperative pain, shorter hospital length of stay, reduced hospital cost, and fewer dressing renewals. A small case-control study compared the outcomes of bone resection alone or in combination with adjuvant antibiotic-impregnated calcium sulphate for the treatment of diabetic foot osteomyelitis in 46 patients who underwent surgical bone resection.[31] A higher postoperative healing rate, longer mean healing duration and lower recurrence rate were recorded in the intervention group, but the authors did not state why calcium sulphate

was used in some cases and not in others. A small controlled before-after study explored if the intraoperative addition of a local vancomycin powder in a series of 38 patients with ulcerated calcaneal osteomyelitis reduced the incidence of surgical revisions and if it was associated with future colonisation by multi-resistant pathogens.[9] After an average follow-up of 26.1 ± 15.0 months, the intervention failed to demonstrate any clinical benefit. Based on the data from 13 studies and a total of 798 patients, a systematic review assessed the role of local antibiotic delivery systems (gentamicin-impregnated sponges, poly methyl methacrylate, calcium sulphate) as an adjunct to surgery in DFIs.[25] Re-operation rates, major amputation, and mortality were similar in patients treated with either antibiotic-eluting devices or standard treatments.

Our new search identified one RCT that examined the use of sodium hypochlorite (also known as Dakin's) solution for irrigation of diabetic foot ulcer infections versus standard rising with normal saline.[19] A total of 90 evaluable hospitalised patients for DFI (45 in each group) were randomly treated with diluted hypochlorite solution (30 min of irrigation each other day) or normal saline for irrigation of diabetic foot ulcer infections in addition to the antibiotic therapy with imipenem/cilastatin or piperacilline/tazobactam. This single-centre trial conducted in Jordan suggests that replacing normal saline irrigation with 0.1% sodium hypochlorite followed by soaking the ulcer with 0.08% sodium hypochlorite (and pursued after hospital discharge) significantly improved ulcer healing and decreased the number of amputations (2.2% vs. 28.9%), hospitalisations and mortality (2.2% vs. 13.3%). Infection resolution rate was higher in the intervention group (35.6% vs. 22.2%) but not statistically significant ($p = 0.17$). The infection severity is not described in either group of participants, neither are the compliance with the saline irrigation or the reasons of the amputations. The single centre design in one geographical location might further diminish the applicability in other centres. Although the effect size is large, these limitations make it very difficult to rely on the conclusions about the superiority of the hypochlorite versus saline irrigations in persons with infected DFIs. Overall, the effects of local antibiotic or antiseptic treatments on the outcomes of DFIs/DFOs are based on low certainty of evidence and the effect size seems small in the majority of studies with the exception of one study to hypochlorite.[19]

Evidence statement

There is insufficient evidence that local antibiotic or antiseptic treatment improves outcomes in diabetic foot infections, except possibly sodium hypochlorite. There is very low-quality evidence that hypochlorite irrigation benefits ulcer healing, amputations and rehospitalisation.

Certainty of evidence

Low, based on retrospective studies and RCTs, all of low quality.

References 2018–2022

Memon 2022,[26] Mendame Ehya 2021,[27] Qin 2019,[31] Brodell 2021,[9] Marson 2018.[25]

References prior to 2018

Uckay, 2018; Uckay, 2018; Lipsky, 2012; Lipsky, 2008; 2017; 2017; Dumville, 2017[72–78]; Martínez-De Jesús, 2007; Piaggesi, 2010; Landsman, 2011;[79–81] Bergqvist, 2016; Jimenez, 2017; Mannucci, 2014,[82–84] Chen, 2008;[85] Jaber 2022.[19]

3.4.2 | Acidifying agents for Pseudomonas

Summary of the literature

One small single-centre pilot case series study examined wound healing and microbial eradication when acidifying agents were applied on the ulcer in 32 patients with DFIs due to *Pseudomonas* species.[11] Clinical and microbial outcomes were comparable when acidifying agents were or were not applied.

Evidence statement

In a patient with diabetes and foot infection due to *Pseudomonas* species, there is currently no evidence of improved wound healing or other clinical benefits from acidifying agents.

Certainty of the evidence

Very low, based on one retrospective cohort study with high risk of bias.

Reference 2018–2022

Fejfarova 2019.[11]

3.4.3 | Rifampicin for DFO

Summary of the literature

In the previous systematic review, 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 DFO.[66] It is very possible that the better outcomes in the group that was treated based on bone biopsy and with rifampicin were 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. In the recent literature search, one large size multicentre retrospective cohort study from the US compared the clinical outcomes of patients treated for DFO with antibiotic regimens that included or did not include rifampicin.[39] The study included 6174 patients with diabetes and osteomyelitis of the foot or ankle, of whom 130 received rifampicin. Amputation or death within 2 years after the diagnosis of DFO was significantly lower in the rifampicin group (35 of 130 [26.9%] vs. 2250 of 6044 [37.2%]; $p = 0.02$). Patients treated with rifampicin were younger, had fewer comorbidities, had received more infectious disease specialty consultations, and had more staphylococcal infections than patients not treated with rifampicin. The logistic regression confirmed the significant

association between rifampicin use and the studied events (0.65; 95% CI, 0.43–0.96; $p = 0.04$). These outcomes need to be confirmed in an RCT currently ongoing in the US before we can advise on the use of rifampicin in patients with DFO.[86] The evidence statement on the benefit of rifampicin treatment in persons with DFO is only based on studies with very high risk of (confounding) bias.

Evidence statement

In a patient with diabetic foot osteomyelitis, available data suggest that rifampicin combination antimicrobial therapy leads to fewer major amputations and lower mortality.

Certainty of evidence

Very low, based on one recent and one older large size multicentre retrospective study with a high risk of bias.

Reference 2018–2022

Wilson 2019.[39]

Reference prior to 2018

Senneville 2008.[66]

3.4.4 | Negative wound pressure therapy for DFIs

Summary of the literature

In the 2020 systematic review,[3] we found insufficient high-quality evidence to assess the effect of negative pressure wound therapy (NPWT) on infection-related outcomes in patients with DFI.[87,88] We identified one study in our recent literature search, that examined the potential impact of using 0.1% polyhexanide-betaine irrigation in NPWT.[23] In a large clinical trial, 150 patients with diabetes and moderate or severe DFIs that required surgical drainage were randomised to receive NPWT either with or without 0.1% polyhexanide-betaine irrigation. The study included hospitalised adults in one medical centre in the USA with wound size 5–100 cm^2. There were no significant differences between the two groups in wound size after index surgery, duration of antibiotics, number of surgeries during the index hospitalisation, duration of NPWT, surgical wound closure, wound dehiscence of surgically closed wounds, proportion of healed wounds, time to wound healing, length of hospitalisation, re-infection, all cause re-hospitalisation, and foot specific re-hospitalisation. Outcomes from this randomised clinical trial suggest no added benefit from using 0.1% polyhexanide-betaine irrigation in NPWT. A recent retrospective study of low quality that included 106 patients with ST-DFIs (some with foot ischaemia) compared the efficacy of surgical debridement with or without use of ultrasound debridement and NPWT in combination with sequential cycles of antiseptic injection into the wound cavity.[34] Control patients were treated with topical tamed iodine solutions and polyethylene glycol ointments with or without foot plastic surgery depending on the foot ulcer outcome. Those treated with ultrasound debridement and NPWT had lower number of major amputations ($p = 0.016$) and reduced length of hospital stay ($p = 0.001$). However, the quality of this study was such that no firm conclusion can be drawn on the beneficial effect of NWPT in DFIs.

Evidence statement

Available data are inconsistent regarding the suggest a potential benefit of in using NPWT with or without irrigation.

Certainty of evidence

Low, based on one RCT with minimal risk of bias and other non-randomised studies.

References 2018–2022

Lavery 2020,[23] Sergeev 2020.[34]

References prior to 2018

Dalla Paola, 2010; Armenio, 2017.[87,88]

3.4.5 | Bioactive glass S53P4 for DFO

Summary of the literature

Two small observational retrospective cohort single-centre studies examined the safety and efficacy of surgical bone debridement and systemic antibiotic therapy with or without filling bioactive glass S53P4 into the infected debrided bone in subjects with DFO.[10,20] The two studies included a total of 66 hospitalised patients in Italy[10] and Slovenia.[20] Both studies differed on the location of DFO (first metatarsophalangeal joint with adjacent bone osteomyelitis vs. different locations of foot osteomyelitis) and the extent of bone resection (limited vs. resection of all the infected bone). While one study[10] found a significantly higher rate of resolution of DFO than in subjects treated with standard treatments (18 [90%] vs. 13 [61.9%], respectively $p = 0.03$) and a lower probability of requiring additional antibiotic therapy, the other study[20] did not find any benefit in terms of infection resolution and ulcer healing in comparison to the standard treatment (10/10 vs. 9/12; $p = 0.22$). The available data on the potential benefit of bioactive glass in persons with DFOs is only based on two low-quality non-randomised studies.

Evidence statement

Limited available data is contradictory about the benefit of bioactive glass S53P4 for the treatment of DFO.

Certainty of evidence

Low, based on two recent small-sized observational retrospective cohort studies with serious risk of bias.

References 2019–2022

DeGiglio 2021[10]; Kastrin 2021.[20]

3.4.6 | Cold atmospheric plasma for DFIs

Summary of the literature

One small RCT examined the effect of application of cold atmospheric plasma or placebo in addition to standard care therapy on wound healing in patients with diabetes and chronic foot ulcer infection.[36] The study included 43 participants from the hospital or ambulatory clinics in Germany. Cold atmospheric plasma therapy yielded a significant increase in wound healing, both in total area reduction and time to relevant wound area reduction. However, there was no significant difference in clinical resolution of infection or microbial burden between cold atmospheric plasma and placebo by the end of treatment. No cold atmospheric plasma therapy-related adverse events occurred during treatment.

Evidence statement

Available data do not suggest improved diabetic foot infection-related outcomes from cold atmospheric plasma.

Certainty of evidence

Low, based on one RCT with high risk of bias.

Reference

Stratmann 2020.[36]

4 | DISCUSSION

In this updated systematic review on interventions for the management of persons with DFIs, the largest number of studies were related to antibiotic treatments for soft-tissue DFIs and DFO. As reported in our previous systematic review,[3] the separation of these two groups is debatable, as the various studies used different definitions for both entities, the percentage of subjects with DFO was sometimes small, and infected bone was removed prior to inclusion in most trials.[3] 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. Finally, this separation appears a bit artificial given that both soft-tissue DFIs and DFO may present concomitantly in a non-negligible proportion of the patients.

We identified a total of 5418 articles published between 2018 and 2022, of which 32 met our inclusion criteria. Overall, the quality of the studies tended to increase in comparison with previous systematic reviews, noting however that there is still a need for more high-quality studies to underpin clinical practice in the management of DFIs. Unfortunately, data about the assessment of new antimicrobials in the settings of DFIs are still very limited, although new antibiotics with activity against multi-resistant strains of staphylococci, enterococci and gram-negative rods have appeared in the last years. New data have emerged regarding the mode of administration of the antibiotic therapy (i.e. intravenous vs. oral route of application) and its duration, especially following surgical intervention for both soft-tissue DFIs and DFO. These data confirm the current international trend to reduce the exposition of patients to the potential negative effects of antibiotics.

We did not find any new studies that addressed the possibility to reduce the 6-week duration of antibiotic therapy for DFO treated medically (without any resection of the infected bones). The new studies we identified confirm that there is a place for conservative treatment of DFO in selected patients and that early surgery is associated with improved outcomes in patients with moderate and severe DFIs. We could not identify clinical trials of sufficient quality that support the use of any topical intervention for the management of DFIs.

In order to improve the quality of future research we suggest that researchers in this area should strictly adhere to the agreed definitions for the diagnosis of soft-tissue DFIs and DFOs, for describing their treatment as well as its outcomes to enable comparison of studies and to translate these findings into recommendations for daily practise.

AUTHOR CONTRIBUTIONS

Edgar J. G. Peters, Éric Senneville, Suzanne A. van Asten, and Zaina Albalawi 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 papers selected for the analysis, and review of the final document.

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CONFLICT OF INTEREST STATEMENT

Prof Senneville has the following disclosures: Honoraria, travel expenses and hospitality for serving on speakers bureaux and advisory boards for Pfizer (Linezolid), MSD (Tedizolid), Novartis-Pharma (Daptomycin), Bayer (Moxifloxacin), Cepheid (GenExpert MRSA-SSTI) and Diaxonhit (BJInoplex), Shionogi (Cefiderocol), Correvio (Dalbavancin), Menarini (Delafloxacin, Meropenem-vaborbactam, Oritavancin), DebioPharm (Afabicin), BioMérieux (JI BioFire), Shionogi (Cefiderocol).

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All other authors have no disclosures.

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

ETHICS STATEMENT

Ethics approval was not required for this study.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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PEER REVIEW

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SUPPORTING INFORMATION

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

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