IWGDF/IDSA Guidelines on the Diagnosis and Treatment of Diabetes-related Foot Infections (IWGDF/IDSA 2023)

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Abstract: The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the management and prevention of diabetes-related foot diseases since 1999. The present guideline is an update of the 2019 IWGDF guideline on the diagnosis and management of foot infections in persons with diabetes mellitus. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was used for the development of this guideline. This was structured around identifying clinically relevant questions in the P(A)ICO format, determining patient-important outcomes, systematically reviewing the evidence, assessing the certainty of the evidence, and finally moving from evidence to the recommendation. This guideline was developed for healthcare professionals involved in diabetes-related foot care to inform clinical care around patient-important outcomes. Two systematic reviews from 2019 were updated to inform this guideline, and a total of 149 studies (62 new) meeting inclusion criteria were identified from the updated search and incorporated in this guideline. Updated recommendations are derived from these systematic reviews, and best practice statements made where evidence was not available. Evidence was weighed in light of benefits and harms to arrive at a recommendation. The certainty of the evidence for some recommendations was modified in this update with a more refined application of the GRADE framework centred around patient important outcomes. This is highlighted in the rationale section of this update. A note is also made where the newly identified evidence did not alter the strength or certainty of evidence for previous recommendations. The recommendations presented here continue to cover various aspects of diagnosing soft tissue and bone infections, including the classification scheme for diagnosing infection and its severity. Guidance on how to collect microbiological samples, and how to process them to identify causative pathogens, is also outlined. Finally, we present the approach to treating foot infections in persons with diabetes, including selecting appropriate empiric and definitive antimicrobial therapy for soft tissue and bone infections; when and how to approach surgical treatment; and which adjunctive treatments may or may not affect the infectious outcomes of diabetes-related foot problems. We believe that following these recommendations will help healthcare professionals provide better care for persons with diabetes and foot infections, prevent the number of foot and limb amputations, and reduce the patient and healthcare burden of diabetes-related foot disease.

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Clinical Infectious Diseases

IDSA GUIDELINES

IWGDF/IDSA Guidelines on the Diagnosis and Treatment of Diabetes-related Foot Infections (IWGDF/IDSA 2023)

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The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was used for the development of this guideline. This was structured around identifying clinically relevant questions in the P(A)ICO format, determining patient-important outcomes, systematically reviewing the evidence, assessing the certainty of the evidence, and finally moving from evidence to the recommendation. This guideline was developed for healthcare professionals involved in diabetes-related foot care to inform clinical care around patient-important outcomes. Two systematic reviews from 2019 were updated to inform this guideline, and a total of 149 studies (62 new) meeting inclusion criteria were identified from the updated search and incorporated in this guideline. Updated recommendations are derived from these systematic reviews, and best practice statements made where evidence was not available. Evidence was weighed in light of benefits and harms to arrive at a recommendation. The certainty of the evidence for some recommendations was modified in this update with a more refined application of the GRADE framework centred around patient important outcomes. This is highlighted in the rationale section of this update. A note is also made where the newly identified evidence did not alter the strength or certainty of evidence for previous recommendations.

The recommendations presented here continue to cover various aspects of diagnosing soft tissue and bone infections, including the classification scheme for diagnosing infection and its severity. Guidance on how to collect microbiological samples, and how to process them to identify causative pathogens, is also outlined. Finally, we present the approach to treating foot infections in persons with diabetes, including selecting appropriate empiric and definitive antimicrobial therapy for soft tissue and bone infections; when and how to approach surgical treatment; and which adjunctive treatments may or may not affect the infectious outcomes of diabetes-related foot problems.

We believe that following these recommendations will help healthcare professionals provide better care for persons with diabetes and foot infections, prevent the number of foot and limb amputations, and reduce the patient and healthcare burden of diabetes-related foot disease.

Keywords. diabetic foot; diagnosis; foot ulcer; guidelines; infection.

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
HBOT	hyperbaric oxygen therapy
HMPAO	Hexa Methyl Propylene Amine Oxime
IDFU	infected diabetes-related foot ulcer
IDSA	infectious diseases society of America
IWGDF	international working group on the diabetic foot
MRI	magnetic resonance imaging

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PACO	population assessment control outcome diabetes-related
PCR	polymerase chain reaction
PCT	procalcitonin
PET	positron emission tomography
PICO	population intervention control outcome
SPECT	single photon emission computed tomography
SR	systematic review
TDM	tomodensitometry

1 LIST OF RECOMMENDATIONS

1. Recommendation 1
   (a) Diagnose a soft tissue diabetes-related infection clinically based on the presence of local or systemic signs and symptoms of inflammation. (Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) recommendation:Strong; Certainty of evidence: Low)
   (b) Asses the severity of any Diabetes-related foot infection (DFI) using the International Working Group on the Diabetic Foot (IWGDF)/Infectious Diseases Society of America (IDSA) classification scheme. (Strong; Low).
2. Recommendation 2
   Consider hospitalising all persons with diabetes and a foot infection who have either a severe foot infection as classified by the IWGDF/IDSA classification or a moderate infection which is associated with key relevant morbidities. (Conditional; Low).
3. Recommendation 3
   Assess inflammatory serum biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or procalcitonin (PCT) in a person with diabetes and a possible infected foot ulcer for whom the clinical examination is diagnostically equivocal or uninterpretable. (Best Practice Statement).
4. Recommendation 4
   For diagnosing diabetes-related foot soft-tissue infection, we suggest not using foot temperature (however measured) or quantitative microbial analysis. (Conditional; Low).
5. Recommendation 5
   In a person with suspected soft tissue DFI, consider a sample for culture to determine the causative microorganisms, preferably by aseptically collecting a tissue specimen (by curettage or biopsy) from the wound. (Conditional; Moderate).
6. Recommendation 6
   Use conventional, rather than molecular, microbiology techniques for the first-line identification of pathogens from soft tissue or bone samples in a patient with a DFI. (Strong; Moderate).
7. Recommendation 7
   In a person with diabetes, consider using a combination of probe-to-bone test, plain X-rays, and ESR, or CRP, or PCT as the initial studies to diagnose osteomyelitis of the foot. (Conditional; Low).
8. Recommendation 8
   Perform magnetic resonance imaging (MRI) when the diagnosis of diabetes-related osteomyelitis of the foot remains in doubt despite clinical, plain X-rays and laboratory findings. (Strong; Moderate).
9. Recommendation 9
   Consider using positron emission tomography (PET), leucocyte scintigraphy, or single photon emission computed tomography (SPECT) as an alternative to MRI for the diagnosis of diabetes-related osteomyelitis of the foot. (Conditional; Low).
10. Recommendation 10
    In a person with diabetes for whom there is a suspicion of osteomyelitis of the foot (before or after treatment), bone (rather than soft tissue) samples should be obtained for culture, either intraoperatively or percutaneously. (Conditional; Moderate).
11. Recommendation 11
    Do not treat clinically uninfected foot ulcers with systemic or local antibiotic therapy when the goal is to reduce the risk of new infection or to promote ulcer healing. Best Practice Statement.
12. Recommendation 12
    (a) Use any of the systemic antibiotic regimens that have been shown to be effective in published randomised controlled trials at standard (usual) dosing to treat a person with diabetes and a soft tissue infection of the foot. (Strong; High).
    (b) Administer antibiotic therapy to a patient with a skin or soft tissue diabetic foot infection for a duration of 1–2 weeks. (Strong; High).
    (c) Consider continuing treatment, perhaps for up to 3–4 weeks, if the infection is improving but is extensive and is resolving slower than expected or if the patient has severe peripheral artery disease (PAD). (Conditional, Low).
    (d) If evidence of infection has not resolved after 4 weeks of apparently appropriate therapy, re-evaluate the patient, and reconsider the need for further diagnostic studies or alternative treatments. (Strong; Low).
13. Recommendation 13
    Select an antibiotic agent for treating a DFI based on the likely or proven causative pathogen(s) and their antibiotic susceptibilities; the clinical severity of the infection; published evidence of the efficacy of the agent for infections

of the diabetes-related foot; the risk of adverse events including collateral damage to the commensal flora; the likelihood of drug interactions; agent availability and costs. Best Practice Statement.

14. Recommendation 14

    Target aerobic gram-positive pathogens only (beta-haemolytic streptococci and *Staphylococcus aureus* including methicillin-resistant strains if indicated) for people with a mild DFI, who have not recently received antibiotic therapy, and who reside in North America or Western Europe. Best Practice Statement.

15. Recommendation 15

    Do not empirically target antibiotic therapy against *Pseudomonas aeruginosa* in cases of DFI in temperate climates, but use empirical treatment of *P. aeruginosa* if it has been isolated from cultures of the affected site within the previous few weeks, in a person with moderate or severe infection who resides in Asia or North Africa. Best Practice Statement.

16. Recommendation 16

    Consider a duration of up to 3 weeks of antibiotic therapy after minor amputation for diabetes-related osteomyelitis of the foot and positive bone margin culture and 6 weeks for diabetes-related foot osteomyelitis without bone resection or amputation. (Conditional; Low).

17. Recommendation 17

    Use the outcome at a minimum follow-up duration of 6 months after the end of the antibiotic therapy to diagnose remission of diabetes-related osteomyelitis of the foot. Best Practice Statement.

18. Recommendation 18

    The urgent surgical consultation should be obtained in cases of severe infection or moderate DFI complicated by extensive gangrene, necrotising infection, signs suggesting deep (below the fascia) abscess, compartment syndrome, or severe lower limb ischaemia. Best Practice Recommendation.

19. Recommendation 19

    Consider performing early (within 24–48 h) surgery combined with antibiotics for moderate and severe DFIs to remove the infected and necrotic tissue. (Conditional; Low).

20. Recommendation 20

    In people with diabetes, PAD and a foot ulcer or gangrene with infection involving any portion of the foot obtain an urgent consultation by a surgical specialist as well as a vascular specialist in order to determine the indications and timings of a drainage and/or revascularisation procedure. Best Practice Statement.

21. Recommendation 21

    Consider performing surgical resection of infected bone combined with systemic antibiotics in a person with diabetes-related osteomyelitis of the foot. (Conditional; Low).

22. Recommendation 22

    Consider antibiotic treatment without surgery in case of (i) forefoot osteomyelitis without an immediate need for incision and drainage to control infection, (ii) without PAD, and (iii) without exposed bone. (Conditional; Low).

23. Recommendation 23

    We suggest not using the following treatments to address DFIs: (a) adjunctive granulocyte colony-stimulating factor (G-CSF) treatment or (b) topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative-pressure wound therapy (with or without instillation). (Conditional; Low).

24. Recommendation 24

    We suggest not using topical (sponge, cream, and cement) antibiotics in combination with systemic antibiotics for treating either soft-tissue infections or osteomyelitis of the foot in patients with diabetes. (Conditional; Low).

25. Recommendation 25

    We suggest not using Hyperbaric oxygen (HBO) therapy or topical oxygen therapy as an adjunctive treatment for the sole indication of treating a DFI. (Conditional; Low).

Note: the available data did not allow making a recommendation on the use of rifampicin for the treatment of diabetes-related osteomyelitis of the foot.

2 INTRODUCTION

The prevalence of diabetes continues to increase globally and the International Diabetes Foundation has estimated that 537 million adults aged between 20 and 79 years worldwide were living with diabetes in 2021.[1] This situation leads to a rising incidence of foot complications, including infections.[1] DFIs are associated with substantial morbidities, requiring frequent healthcare provider visits, daily wound care, antimicrobial therapy, surgical procedures, and high healthcare costs.[2] Of particular importance, DFIs remain the most frequent diabetes-related complications requiring hospitalisation and the most common precipitating events leading to lower extremity amputation.[3,4] Outcomes in patients presenting with an infected diabetes-related foot ulcer (DFU) are suboptimal in one large prospective study, at the end of 1 year, the ulcer had healed in only 46% (and it later recurred in 10% of these), while 15% had died and 17% required a lower extremity amputation.[5]

Managing DFIs requires careful attention to properly diagnose the condition, obtain appropriate specimens for culture, thoughtfully select antimicrobial therapy, quickly determine when surgical interventions are required, and provide any needed additional wound and overall patient care. A systematic,

evidence-based approach to managing DFIs likely improves outcomes, specifically the resolution of difficult cases of infection, and helps avoid complications, such as life-threatening infections and limb loss. This is best delivered by interdisciplinary teams, which should include among the membership, whenever possible, infectious diseases or clinical/medical microbiology specialist.[6] This team should also attempt to ensure optimal local wound care (e.g., cleansing and debridement), pressure off-loading, peripheral vascular assessment (with revascularisation if needed), and metabolic (particularly glycaemic) control. For these aspects, the reader is referred to the other chapters of the IWGDF guideline on the management of diabetes-related foot ulcers in this special issue.[7–9] If these aspects are not adequately addressed, and the focus is only on infection, the chance of treatment failure is greatly increased.

Several guidelines are available to assist clinicians in managing DFIs. The IDSA produced a guideline in 2004, which was updated in 2012.[10,11] A panel of experts convened by IWGDF has published widely used guideline documents quadrennially since 2004.[12] The present 2023 edition of the IWGDF guidelines on the management of DFI updates the content of the 2019 edition on the diagnosis and treatment of DFIs and is part of the aforementioned guidelines.[13] The IWGDF and IDSA have now agreed to provide a combined intersociety guideline on the diagnosis and treatment of DFIs; as a result, the expert panel involved in the creation of the new guideline document included for the first time members from both IWGDF and IDSA working on a single document.

3 BACKGROUND

Infections of the skin and soft tissues of the foot in a person with diabetes most often follow a break in the protective skin envelope. The most common such break is a DFU, which usually involves at least the epidermis and part of the dermis. This complication most often occurs in those with peripheral neuropathy, and frequently those with PAD.[14] Infection follows the colonisation of the wound by a complex microbiological flora. Wound colonisation by bacteria is a constant phenomenon, defined by the presence of bacteria on the wound surface but without evidence of invasion of the host tissues. Wound infection is a pathological state caused by the invasion and multiplication of microorganisms in host tissues that induce an inflammatory response, usually followed by tissue damage. Since all wounds are colonised (often with potentially pathogenic microorganisms), wound infection cannot be defined using only the results of wound cultures. Instead, DFIs are defined clinically based on the presence of manifestations of an inflammatory process involving a foot wound located below the malleoli. In persons with diabetes-related foot complications, signs and symptoms of inflammation may, however, be masked by the presence of peripheral neuropathy, PAD, or immune dysfunction. A patient with diabetes-related complications may need to undergo lower extremity amputation to control infection or develop multiorgan failure without local clinical signs that define a DFI, but this is highly uncommon. Although rarely the primary cause of foot ulcers, the presence of PAD increases the risk of an ulcer becoming infected[4,15–17] and adversely affects the outcome of infection.[4,18,19] Because the combination of infection with PAD is associated with a markedly increased risk of poor healing and amputation, clinicians should evaluate the state of wound perfusion and the potential need for a revascularisation procedure as soon as possible in all patients with a DFI.[7]

Factors that predispose to foot infection include having a wound that is deep, long-standing, recurrent, or of traumatic aetiology; the presence of diabetes-related immunological perturbations, particularly neutrophil dysfunction; and having concomitant chronic renal failure.[16,18–23] Although examined in only a few studies, a history of chronic hyperglycaemia may predispose to DFIs, and the presence of hyperglycaemia at presentation may suggest a rapidly progressive or destructive (necrotising) infection.[24,25]

While most DFIs are relatively superficial at presentation, microorganisms can spread contiguously to subcutaneous tissues, including fascia, tendons, muscles, joints, and bones. The anatomy of the foot, which is divided into several separate but intercommunicating compartments, fosters the proximal spread of infection.[26] The inflammatory response induced by infection may cause compartmental pressure to exceed capillary pressure, leading to ischaemic tissue necrosis in the affected compartment and thereby progressive infection.[27,28] The tendons within the compartments facilitate the proximal spread of infection, which usually moves from higher to lower pressure areas. Bacterial virulence factors may also play a role in these complex infections.[29,30] Systemic symptoms (e.g., feverishness or chills), marked leucocytosis, or major metabolic disturbances are uncommon in patients with a DFI, but their presence denotes a more severe, potentially limb-threatening (or even life-threatening) infection.[4,31,32] If not quickly diagnosed and properly treated, DFIs tend to progress, sometimes rapidly.[33] Thus, an experienced medical specialist (or team) with experience in infectious diseases should evaluate a patient with a severe DFI within 24 h[34] Accumulations of purulent secretions, especially if under pressure or associated with necrosis, require prompt (usually within 24 h) surgical decompression and drainage. Although bone and/or joint resection (preferably using a conservative approach, with limited resection and avoiding amputation, if possible) may be required for successfully treating osteomyelitis, it is usually an infection of the soft tissues that requires urgent antimicrobial therapy and surgical intervention.

This document aims to provide a comprehensive, evidence-based overview of guidelines for the diagnosis and treatment of foot infections in people with diabetes. These are intended to be

of practical use for treating clinicians based on all available scientific evidence.

4 METHODOLOGY

The GRADE framework was used for developing this guideline.[35] This is structured around identifying key clinical questions in the Population, Assessment, Comparison, Outcome and patient/population, intervention, comparison, outcomes format, determining patient-important outcomes, presenting the evidence, assessing the certainty of the evidence, and finally moving from evidence to the recommendation.

The IWGDF editorial board appointed a multidisciplinary working group of independent experts (the authors of this guideline) to update the previously published 2019 guidelines. In addition, three members were delegated by the IDSA to join the committee.

The key clinical questions were developed by revising the 2019 guideline PICOs and refining each component to reflect clinical relevance. Guidance is aimed at clinicians and other healthcare professionals involved in the diagnosis and management of DFIs. Patient important outcomes were generated and then classified based on their importance for decision-making. Outcomes defined by Jeffcoate et al were also used as a reference guide.[36] All members voted on the outcomes, and those identified by consensus as "critically important" were included. The editorial board reviewed and approved the final set of P(A)ICOs through a consultation process with external experts from various geographical regions and the IDSA.

The committee members then systematically reviewed the literature to address the set of pre-specified P(A)ICOs. The two updated IWGDF systematic reviews supporting this guideline have been completed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, which will be published separately.[37] The updated protocols are available from PROSPERO (CRD42022324795, CRD42022324812).[38,39]

After careful weighing of the summary of judgments, the same teams of two members of the working group determined the direction, strength, and wording of the recommendation(s) for the specific clinical question. Recommendations aimed to be clear, specific, and unambiguous on what was recommended, for which persons, and under what circumstances. Recommendations were rated as 'for' or 'against' the particular intervention or 'either the intervention or the comparison', and the strength of each recommendation was rated as 'strong' or 'conditional'. The certainty of evidence, rated as 'high', 'moderate', 'low' or 'very low' based on the critical outcome(s) reviewed for the question in accordance with GRADE, as explained above, was added to the strength of the recommendation.

Summary of judgements tables and recommendations for each question were extensively discussed in online meetings of the working group. After discussion, a voting procedure was used for each recommendation to grade the direction of the recommendation as 'for' or 'against' the particular intervention (or 'either the intervention or the comparison'), and the strength of each recommendation as 'strong' or 'conditional'. A quorum of 60% of members was needed to be present for a discussion and vote to go ahead and a majority vote of those present was needed for final decisions on each recommendation. The outcomes of the voting are provided in the summary of judgement tables in the supplemental information of the guideline documents.

Based on the summary of judgement tables, the rationales for the recommendations were written by the same team of two assessors of the working groups. These rationales are narrative (systematic) descriptions of how the working group came to the direction and strength of the recommendation and summarises the research evidence for the items in the summary of judgement tables.[35,40] In addition, expert opinion, and aspects relevant to communicating to the reader regarding the intervention or recommendation can be added to these rationales.

Finally, all recommendations, with their rationales, were collated into a consultation (draft) guideline manuscript that was reviewed by the same international external experts and persons with lived experience who reviewed the clinical questions and outcomes, as well as by the IWGDF Editorial Board. The working group then collated, reviewed and discussed all feedback on the consultation manuscript and revised accordingly to produce the final guidelines.

In the publication "Standards for the development and methodology of the 2023 IWGDF guideline", the details of the methodology for the development of this guideline are described.[41]

5 RECOMMENDATIONS

See Figure 1 for a synthesising overview of the overall diagnosis and management of patients with DFIs, including diabetes-related osteomyelitis of the foot.

5.1 Diagnosis

5.1.1 Clinical question

Can the International Working Group of the Diabetic Foot/IDSA (IWGDF/IDSA) classification system for foot infections in persons with diabetes predict the outcome of such an infection?

Recommendation 1.

(a) Diagnosis of a soft tissue diabetes-related infection clinically based on the presence of local or systemic signs and symptoms of inflammation. (Strong; Low)

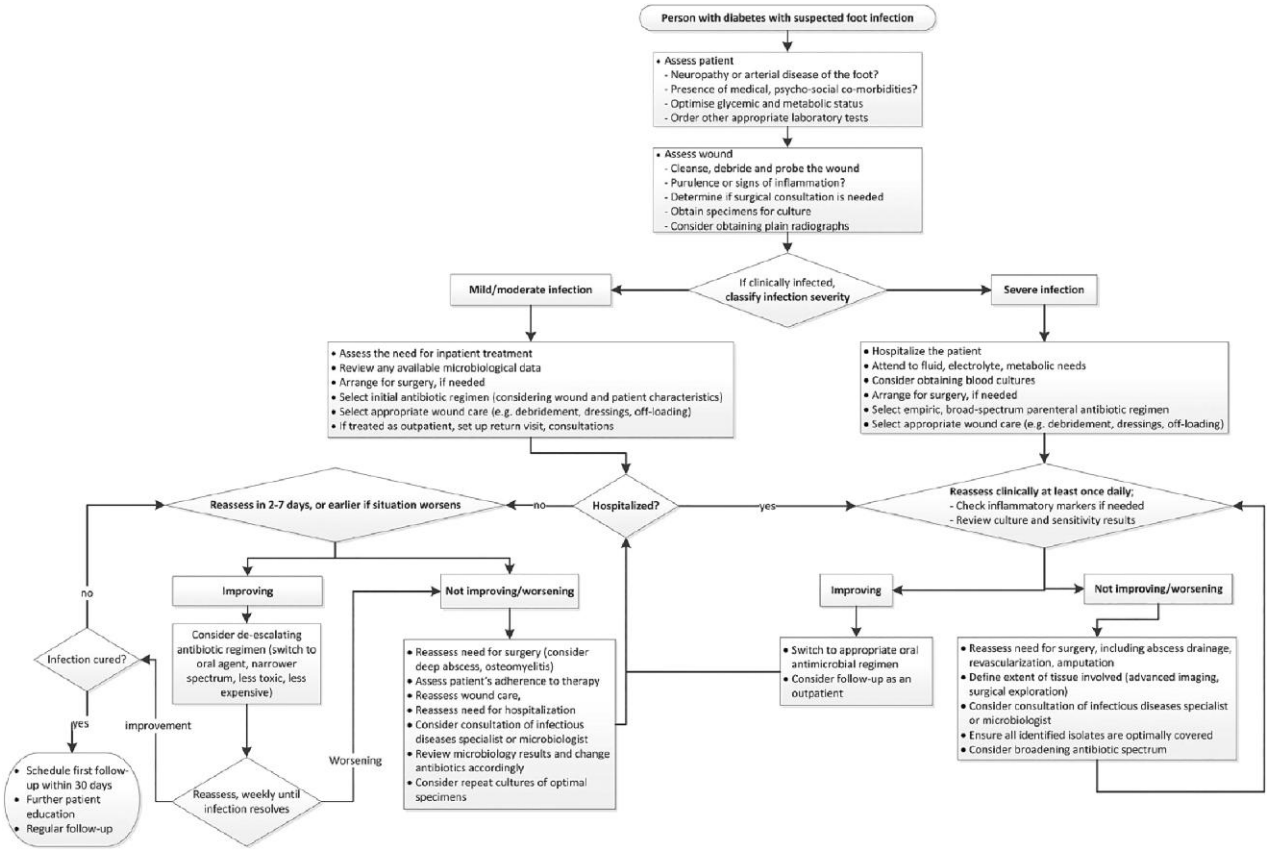

Figure 1. An overview of the diagnosis and management of patients with Diabetes-related foot infections (DFIs) (from Lipsky et al. DMRR 2019). Perform non-invasive bedside test for peripheral artery disease (PAD).

(b) Assess the severity of any DFI using the IWGDF/IDSA classification scheme. (Strong; Low).

Rationale. The clinician seeing a patient with diabetes and a foot ulcer should always assess for the presence of an infection and, if present, classify the infection's severity.[42,43] Experts have proposed many classification schemes for DFU, many of which only include the presence or absence of "infection".[9] Previous prospective and retrospective studies have validated all or part of the IWGDF/IDSA DFI classification as part of a larger diabetes-related foot classification system (PEDIS) (see Table 1).[4,15] Other classifications for severe infection, for example, National Early Warning Score[44,45] or quick sequential organ failure assessment,[46] were developed for the identification or prediction of outcomes in patients with sepsis. However, there are no data to support changing from using the systemic inflammatory response syndrome (SIRS) that is part of the IWGDF/IDSA classification to any other classification for DFIs. Two commonly used classifications for DFUs, Wound, Ischaemia, and foot Infection, and Site, Ischaemia, Neuropathy, Bacterial Infection, and Depth, which use the IWGDF/IDSA classification for the infection component, have been validated with patient data.[47,48]

Importantly, in the current guideline, we define a DFI based on the presence of evidence of (a) inflammation of any part of the foot, not just of an ulcer, or (b) findings of SIRS. Because of the important diagnostic, therapeutic, and prognostic implications of osteomyelitis, we separated it out by indicating the presence of bone infection with "(O)" after the grade number (3 or 4) (see Table 1). We did not use the term osteitis, which would be an infection of the cortical bone only, without the involvement of the medulla. Although the pathogens enter the bone through contiguous spread from an ulcer to the cortex and not by haematological spread to the medulla, it is difficult to distinguish the cortical bone infection from medullary bone infection clinically by imaging or histology. Also, we think that the two entities do not require separate therapeutic interventions. Therefore, we decided to use the term osteomyelitis for both disease entities.

In our systematic review on the diagnosis of foot infection in persons with diabetes,[49] new studies with a high risk of bias were identified that examined the outcomes of interest.[50–54] The main questions addressed concerned whether there should

Table 1. The classification system for defining the presence and severity of foot infection in a person with diabetes.[a]

Clinical classification of infection, definitions	IWGDF/IDSA classification
No systemic or local symptoms or signs of infection	1/Uninfected
Infected: At least two of these items are present: • Local swelling or induration • Erythema >0.5 but <2 cm[b] around the wound • Local tenderness or pain • Local increased warmth • Purulent discharge	2/Mild
And, no other cause of an inflammatory response of the skin (e.g., trauma, gout, acute charcot neuro-arthropathy, fracture, thrombosis, or venous stasis)	
Infection with no systemic manifestations and involving: • Erythema extending ≥2 cm[b] from the wound margin, *and/or* • Tissue deeper than skin and subcutaneous tissues (e.g., tendon, muscle, joint, and bone)[c]	3/Moderate
Infection involving bone (osteomyelitis)	Add "(O)"
Any foot infection with associated systemic manifestations (of the systemic inflammatory response syndrome [SIRS]), as manifested by ≥2 of the following: • Temperature, > 38°C or <36°C • Heart rate, > 90 beats/min • Respiratory rate, > 20 breaths/min, *or* PaCO2 < 4.3 kPa (32 mmHg) • White blood cell count >12,000/mm^3, *or* < 4G/L, *or* >10% immature (band) forms	4/Severe
- Infection involving bone (osteomyelitis)	Add "(O)"

The presence of clinically significant foot ischaemia makes both diagnosis and treatment of infection considerably more difficult.

[a]infection refers to any part of the foot.

[b]in any direction, from the rim of the wound.

[c]if osteomyelitis is demonstrated in the absence of ≥2 signs/symptoms of local or systemic inflammation, classify the foot as either grade 3(O) (if <2 SIRS criteria) or grade 4(O) if ≥2 SIRS criteria) (see text).

be modifications of the current IDSA/IWGDF classification by combining the moderate and severe categories and considering risk categories according to soft tissue infections or osteomyelitis. Insufficient quality of evidence led us to not consider either laboratory risk indicators for necrotising fasciitis or SIRS as reliable tools for predicting lower extremity amputation, mortality, or other health outcomes.[52,53] In the absence of additional validation studies, and moderate certainty attributed to the risk of bias, we elected not to alter the IDSA/IWGDF classification, as shown in Table 1.

Defining the infection of the foot in persons with diabetes is of utmost importance, given the possible negative consequences of missing this diagnosis. Additionally, distinguishing infected from non-infected wounds may help avoid the unnecessary use of antibiotics in the absence of infection. Although based on low quality of evidence given the major impact, the use of the IWGDF/IDSA classification may have on outcome and antibiotic use in persons with DFIs, we made a strong recommendation.

Recommendation 2. Consider hospitalising all persons with diabetes and a foot infection who have either a severe foot infection as classified by the IWGDF/IDSA classification or a moderate infection which is associated with key relevant morbidities. (Conditional; Low).

Rationale. Regarding the decision to hospitalise a patient with a DFI, the IWGDF/IDSA infection classification system facilitates risk stratification to inform this decision.[4] Hospitalisation is an expensive and finite resource and may subject the patient to major inconvenience and potential nosocomial risks. But while many patients with a DFI do not need to be hospitalised, some certainly should be. The consideration should be given to hospitalise all persons with a severe foot infection to ensure timely and effective management, as well as those with a moderate infection associated with key relevant co-morbidities, in particular, PAD (see details in Table 2). This is due to a higher risk of poor outcomes in these cases, especially amputation or death.[4,16,17,19] Of note, the presence of osteomyelitis does not necessarily require hospitalisation, since many of these patients are clinically stable and can be treated with oral antibiotic agents. Hospitalisation may be preferable (at least initially) in those patients who require intravenous antibiotic therapy, have substantial associated soft tissue infection, require special diagnostic testing, or require urgent surgical treatment. Fortunately, almost all patients with a mild infection, and many with a moderate infection but without any key relevant morbidities, can be treated in an ambulatory setting. The availability of home parenteral antibiotic programs in some countries is another site-dependent factor that influences the need for hospitalisation.

Most published studies of DFIs have enrolled hospitalised patients, but over the past 2 decades, several have reported good results with outpatient treatment.[51–53] Therefore, it is of utmost importance to correctly assess the infection severity as the patient management significantly differs from oral antibiotic treatments to complex combinations of surgery and parenteral broad-spectrum antibiotic regimens. Given the low certainty of the evidence, with inconsistency between studies, and the fact that differences in patient characteristics as well as health care policies between countries will influence the decision to hospitalise, we made a conditional recommendation.

Recommendation 3. Assess inflammatory serum biomarkers such as CRP, ESR, or PCT in a person with diabetes and a possible infected foot ulcer for whom the clinical examination is diagnostically equivocal or uninterpretable. (Best Practice Statement).

Rationale. Serum tests for inflammatory biomarkers such as white blood cell (WBC) count, ESR, CRP, and PCT are widely available, easily obtained, and most, except PCT, are relatively

Table 2. Characteristics suggesting a more serious diabetes-related foot infection (DFI) and potential indications for hospitalisation.[4,16–18]

A. Findings suggesting a more serious diabetes-related foot infection	
Wound specific	
Wound	Penetrates to subcutaneous tissues (e.g., fascia, tendon, muscle, joint, or bone)
Cellulitis	Extensive (>2 cm), distant from ulceration, or rapidly progressive (including lymphangitis)
Local signs/symptoms	Severe inflammation or induration, crepitus, bullae, discolouration, necrosis or gangrene, ecchymoses or petechiae, and new anaesthesia or localised pain
General	
Presentation	Acute onset/worsening or rapidly progressive
Systemic	Fever, chills, hypotension, confusion, and volume depletion
Laboratory tests	Leucocytosis highly elevated C-reactive protein, or erythrocyte sedimentation rate, severe or worsening hyperglycemia, acidosis, new/worsening azotaemia and electrolyte abnormalities tests
Complicating features	Presence of a foreign body (accidently or surgically implanted), puncture wound, deep abscess, arterial or venous insufficiency, lymphoedema, immunosuppressive illness or treatment, acute kidney injury
Failing treatment	Progression while on apparently appropriate antibiotic and supportive therapy

B. Factors that should lead to considering hospitalisation
Severe infection (see findings suggesting a more serious diabetes-related foot infection above)
Metabolic or haemodynamic instability
Intravenous therapy needed (and not available/appropriate as an outpatient)
Diagnostic tests needed that are not available as an outpatient
Severe foot ischaemia is present
Surgical procedures (more than minor) required
Failure of outpatient management
Need for more complex dressing changes than patient/caregivers can provide
Need for careful, continuous observation

inexpensive. A few studies have investigated other inflammatory markers for their role in diagnosing or following DFIs, but they were small and of low quality.[11] Most available studies assessed the value of these inflammatory biomarkers by comparing them with the results of IDSA/IWGDF criteria for infection.[4,54] Unfortunately, the severity of infection in patients included in the available studies was not always clearly defined, which may account for interstudy differences in findings. In addition, many studies do not specify if enroled patients were recently treated with antibiotic therapy, which could affect results.[55] Of particular note is the WBC level, as it is used as part of the IDSA/IWGDF criteria for classifying infection as severe/grade 4. The available studies[56–61] found little correlation of WBC with infection severity, with about half of the patients diagnosed with a DFI having a normal WBC.[60,61] In most studies, ESR values have been higher in patients with an infected DFU compared with a noninfected DFU.[56,57] ESR values can be affected by various co-morbidities (e.g., anaemia and azotaemia) and may not be elevated in acute infections due to the relatively slow response of this inflammatory biomarker. A highly elevated ESR (≥70 mm/h) has a sensitivity, specificity, and AUC for the diagnosis of DFO of 81%, 80%, and 0.84, respectively.[62]

Compared with ESR, CRP levels tend to rise more quickly with infection and fall more quickly with the resolution of infection. Serum values of CRP have consistently been found to be significantly higher in infected than noninfected DFUs and in patients with noninfected DFU than in those with no foot ulcer, with levels increasing significantly with the severity of infection.[62,63] Compared to WBC and ESR, CRP has shown higher diagnostic accuracy for grade 2 (infected) DFU.[63] Studies of serum PCT levels have also found that levels were significantly higher in infected DFU than noninfected DFU, but there was little correlation between the values and the infection severity.[54,57,58,64,65] The highly variable cut-off values used make it difficult to interpret the results reported in studies that have investigated these inflammatory markers. Due to their limited specificity and sensitivity, not exceeding 0.85, when used as sole diagnostic tools, inflammatory biomarkers should be used when uncertainty persists after clinical assessment. We make a Best Practice Statement about the use of ESR, CRP, or PCT due to the potential harms related to potential over or underdiagnosing DFI, with low certainty of evidence based on studies of low quality, with inconsistency about the results and heterogeneity in cut-off values.

Recommendation 4. For diagnosing diabetes-related foot soft-tissue infection, we suggest not using foot temperature (however measured) or quantitative microbial analysis. (Conditional; Low).

Rationale. While various imaging tests are widely used for diagnosing bone infection (see below), there are few data on their usefulness for soft-tissue infections. Other diagnostic

tests studied for assessing DFI include photographic foot imaging and infrared thermography. Several studies with these instruments have examined their value in predicting the occurrence of foot ulcerations. Overall, employing either infrared or digital thermography does not appear to provide substantial help in diagnosing infection or predicting the clinical outcome in patients with a DFU seen in the hospital setting.[66–69] While infrared imaging likely causes no harm, its use is limited by low availability.

Some advocate using the presence of high numbers of bacteria on culture (usually defined as $\geq 10^5$ colony-forming units per gram of tissue) as a basis for differentiating infected from uninfected DFUs.[70,71] However, there is no convincing data (from studies using either conventional culture or molecular methods) supporting this concept.[72] In published studies that assessed the validity of clinical signs for the diagnosis of DFI using microbial analysis as a referent test, the criteria used to define infection varied among the authors, and even between studies conducted by the same team. In some microbial analysis studies, patients receiving antibiotics at the time of the wound sampling (which may suppress bacterial growth and cause diminished organism counts) were included, while others failed to provide information on this important confounding issue. Of note, these methods for measuring what is sometimes called "wound bioburden" are time-consuming and relatively expensive. Furthermore, neither quantitative classical culture nor molecular quantitative techniques are currently available to most clinicians in their daily care of patients. Our recommendation against these diagnostic methods is based on the limited data to support the use of these time- and resource-consuming techniques, which are frequently unavailable, and may lead to overdiagnosing (and unnecessarily treating) IDFU. The recommendation is conditional based on low certainty of evidence.

5.1.2 Clinical question

In a person with diabetes and infection of the foot, which test(s) can best identify the causative pathogen(s), and result in tailored use of antibiotics?

Recommendation 5. In a person with suspected soft tissue DFI, consider a sample for culture to determine the causative microorganisms, preferably by aseptically collecting a tissue specimen (by curettage or biopsy) from the wound. (Conditional; Moderate).

Rationale. In the great majority of cases, obtaining a specimen (after cleansing and debridement and trying to avoid contamination) for culture from a DFI provides useful information on the causative pathogen(s) and their antibiotic susceptibility, allowing appropriate selection of antibiotic therapy. In cases of an acute, non-severe DFI in a patient who has not recently received antibiotic therapy and has no other risk factors for unusual or antibiotic-resistant pathogens (e.g., based on specific exposures or previous culture results), selecting empiric therapy without culture may be reasonable. In other situations, despite superficial swabs being easier to perform, we advise collecting a soft tissue specimen on the basis of two systematic reviews[73,74] (with low-quality evidence), one small prospective study[75] and one well-designed prospective study,[76] which reported higher sensitivity and specificity of tissue specimens for culture results than superficial swabs. Collecting a tissue specimen may require slightly more training and pose a slight risk of discomfort or bleeding, but we believe the benefits clearly outweigh this minimal risk of harm. The evidence informing which method of specimen collection to use is limited by the absence of a definitive criterion standard for defining the ulcer infection.

Repeating cultures may be useful for a patient who is not responding to apparently appropriate therapy, but this may result in isolating antibiotic-resistant strains likely to be contaminants rather than pathogens. A key caveat is that the accuracy of culture results depends on the quality of the information provided between clinical and microbiology staff throughout the sample pathway, from collecting, to transporting, to processing and reporting. Clinicians should provide key clinical details associated with the patient and the sample, and clinical microbiology services should provide adequate comprehensive and clear reporting of the isolated organisms and their susceptibility profiles. For persons presenting in a low-income limited resource setting without ready access to culture or follow-up care, performing a Gram-stained smear of material from a DFI could be a relatively easy and inexpensive way to visualise the class of the likely causative pathogens, thus helping direct empiric therapy.[77] The recommendation is conditional with a moderate certainty of evidence based on clinical studies with varying quality, including one large prospective study.

Recommendation 6. Use conventional, rather than molecular, microbiology techniques for the first-line identification of pathogens from soft tissue or bone samples in a patient with a DFI (Strong; Moderate).

Rationale. Molecular microbiology techniques have demonstrated that the flora in most DFIs is more diverse and abundant than that revealed using conventional culture methods.[78–82] Our systematic review identified 4 recent single-centre prospective studies that compared the results of different non-culture (molecular microbiological) methods to those of conventional culture.[49,83–86] These studies addressed this question in both skin and soft-tissue infections and osteomyelitis of the foot. They consistently found an agreement of more than 0.70 between molecular microbiology and conventional culture methods regarding the most clinically relevant pathogens identified, except for anaerobes, which are more frequently

identified by non-culture techniques.[82] The studies also confirmed that non-culture techniques, especially metagenomic next-generation sequencing (mNGS) (NGS), identify more bacteria from tissue samples, including bone, than conventional cultures.[83–86] Currently, the use of mNGS techniques does not lead to a shorter time until pathogen identification, but this might change with the deployment of newer techniques. These techniques may help choose the empirical antibiotic therapy and reduce the risk of inappropriate treatment (i.e., failing to cover bacteria involved, including multiresistant ones). On the other hand, as molecular microbiology techniques are currently unable to distinguish dead from living bacterial cells, there are concerns that they may lead to the unjustified use of broad-spectrum antibiotics. The studies that addressed molecular microbiology for either STI or DFO included relatively few subjects, were at high risk of bias, and did not provide information on the value of the findings for guidance on clinical management. Specifically, we do not know which of the many bacterial genera identified using molecular methods contribute to the clinical state of infection or require targeted antibiotic therapy. Overall, we acknowledge the essential role of molecular microbiology techniques in the understanding of the pathophysiology of DFIs, and that these are promising techniques for application in clinical practice in the future. We do not, however, recommend their use in daily practice, given the unclear significance of positive results, absence of demonstrated impact on antibiotic treatment, high costs, and limited availability. This is a strong recommendation against the use of non-culture techniques, based on a moderate certainty of evidence from prospective studies with a high risk of bias, the relative high costs and the lack of information to what extent these techniques will influence clinical management. Thus, for now, clinicians should continue to request conventional cultures of specimens to determine the identity of causative microorganisms and their antibiotic sensitivities.

5.1.3 Clinical question

In a person with diabetes and suspected bone or joint infection of the foot, which tests have the best correlation with BonE BiOPsy (BeBoP) results for diagnosing diabetes-related osteomyelitis, including residual/postoperative osteomyelitis)?

Recommendation 7. In a person with diabetes, consider using a combination of probe-to-bone test, plain X-rays, and ESR, or CRP, or PCT as the initial studies to diagnose osteomyelitis of the foot. Conditional; Low.

Rationale. The diagnosis of osteomyelitis in the foot of a person with diabetes may be difficult partly because of a lack of a universally accepted definition or criterion standard, and partly related to low levels of inter-test agreement among commonly used diagnostic tests.[87] Osteomyelitis may be present underlying any foot wound, especially those that have been present for many weeks or that are wide, deep, located over a bony prominence, showing visible bone, or accompanied by an erythematous, swollen ("sausage") toe.[88]

Diagnosis of bone infection of the foot is of paramount importance, given that its presence greatly increases the risk of minor and major amputations. The investigation of diabetes-related foot wounds suspected of having bone infection usually includes a physical examination and a conventional radiograph, while some blood biomarkers might be of interest; these issues are discussed below. An accurate diagnosis of DFO is essential to initiate appropriate therapy and to avoid unjustified prolonged antibiotic treatment and surgery in patients who do not have a DFO.

Probe-to-bone test

Among clinical examinations of the foot, the PTB test is the most useful, but the performing clinician's technique and experience, the location of ulcer, and its aetiology may affect the test reliability.[89,90] A systematic review of the PTB test found that for detecting DFO, the sensitivity was 0.87 and specificity 0.83.[91] Overall, in diagnosing DFO, the PTB test suggests the diagnosis if it is positive in a high-risk patient and helps rule it out if it is negative in a low-risk patient. The procedure is easy to learn and perform, requiring only a sterile blunt metal probe (gently inserted into the wound, with a positive test defined by feeling a hard, gritty structure), is inexpensive and essentially harmless, but interobserver agreement is only moderate.[92] Of note, if clinicians are not skilled in this test, they should not rely on its results as it may have been performed incorrectly, resulting in incorrect results.

Plain X-ray

Any patient with a possible bone infection should initially have plain X-rays of the foot. Interpreted by an experienced reader, characteristic findings of bone infection (see Table 3) are highly suggestive of osteomyelitis, but similar abnormal findings can be caused by Charcot osteoarthropathy and other disorders. As plain X-rays are relatively inexpensive, widely available, and cause minimal harm, we recommend them as part of the routine assessment of patients presenting with a DFI. This imaging exam provides useful information, especially about the status of the underlying osteoarticular tissues, the presence of gas in deep tissues, and the presence of any radio-opaque foreign body. In addition, the image can be used as a reference against which to compare new images if the patient presents with another foot problem. Because plain X-rays are insensitive to acute osteomyelitis, it is often useful to repeat a normal examination in 2–3 weeks when the suspicion of osteomyelitis is still high.[93] A retrospective study of patients with histologically proven DFO found that after adjusting for confounders, inflammatory biomarkers, and plain X-rays were actually

Table 3. Features characteristic of diabetes-related osteomyelitis of the foot on plain X-rays.

• New or evollistaving radiographic features[a] on serial radiographs,[b] including: o Loss of bone cortex, with bony erosion or demineralisation o Focal loss of trlistaabecular pattern or marrow radiolucency (demineralisation) o Periosteal reaction or elevation
• Bone sclerosis, with or without erosion
• Abnormal soft tissue density in the subcutaneous fat, or gas density, extending from skin towards underlying bone, suggesting a deep ulcer or sinus tract
• Presence of sequestruma: devitalised bone with radiodense appearance separated from normal bone
• Presence of involucrum[a]: layer of new bone growth outside previously existing bone resulting, and originating, from stripping off the periosteum
• Presence of cloacae[a]: opening in the involucrum or cortex through which sequestrum or granulation tissue may discharge

[a]some features (e.g., sequestrum, involucrum, and cloacae) are seen less frequently in diabetes-related foot osteomyelitis than in younger patients with osteomyelitis of larger bones.

[b]usually spaced several weeks apart.

more useful than MRI.[94] Because interpretation of plain X-rays can be difficult (even for an experienced reader) when non-infectious changes (especially those related to neuro-osteoarthropathy) are present, advanced imaging techniques or even bone culture may ultimately be needed to confirm or exclude osteomyelitis in the foot.

Serum biomarkers

In a systematic published in 2019, it was found that ESR ≥70 mm/hr had a sensitivity, specificity, and AUC of 0.81, 0.8 and 0.84, respectively, while the value of PCT could not be assessed due to paucity of the data.[62]

A more recent systematic review and meta-analysis published in 2022 found that PCT had the highest diagnostic test accuracy when compared to that of ESR, WBC and ESR with sensitivity, specificity, and AUC of 0.85, 0.67 and 0.844 at a cut-off value of 0.33 ng/mL.[63,95] Given the lack of inter-operator variability, the use of either ESR, CRP, or PCT as a sole biomarker for the detection of DFO in a patient with soft tissue DFI is not appropriate, but their use in combination with other diagnostic tests may be useful. A large-scale retrospective single-centre study with high risk of bias that used the results of culture and/or histology of bone samples as a reference standard found that ESR >60 mm/hr plus CRP ≥80 mg/L had a high positive predictive value, but a modest negative predictive value, for the diagnosis of DFO.[96] In another study, the combination of elevated ESR (>43 mm/h) with a positive PTB test showed a high correlation with having positive bone culture and/or histology results.[97]

Overall, neither plain x-ray, inflammatory biomarkers (ESR, CRP and PCT) nor probe-to-bone tests can one their own solely and reliably rule in or rule out the diagnosis of DFO. When diagnostic doubt persists after the clinical assessment and review of plain X-rays of the foot, we recommend testing for ESR, CRP, or PCT. However, this recommendation is conditional because of the risk of over- or under-diagnosis of bone infection, based on a low quality of evidence with inconsistency in the data on diagnostic accuracy results.

Recommendation 8. Perform MRI when the diagnosis of diabetes-related osteomyelitis of the foot remains in doubt despite clinical, plain X-rays and laboratory findings. (Strong; Moderate).

Recommendation 9. Consider using PET, leucocyte scintigraphy, or SPECT as an alternative to MRI for the diagnosis of diabetes-related osteomyelitis of the foot. (Conditional; Low).

Rationale. Depending on the patient setting, advanced imaging for diagnosing osteomyelitis is not needed in many patients. When needed, MRI has been the most commonly ordered advanced imaging technique to diagnose DFO, with moderate costs (but about 10 times higher than that of plain X-rays) and wide availability in high-income countries. Besides being used as a (very sensitive) diagnostic tool, MRI gives a good overview of the anatomy of soft tissues as well as bones and joints, which can be of aid for detecting pre-operatively any purulent collections or the extent of bone involvement. Among advanced imaging techniques, MRI has been the most studied, is associated with lower costs than some other advanced imaging techniques, and gives an overview of the presence and extent of both soft tissue and bone infections in the foot.[98,99] It is important to note that the presence of reactive bone marrow oedema from non-infectious pathologies, such as trauma, previous foot surgery or Charcot neuroarthropathy, lowers its specificity and positive predictive value.[100,101] In selected patients with possible neuro-osteoarthropathy, newer techniques such as MR angiography, dynamic contrast-enhanced MRI or neurography may better distinguish Charcot arthropathy from osteomyelitis.[102–105] The accuracy of MRI findings can be improved by using the results of a second read by an expert musculoskeletal radiologist.[107] Another finding likely to augment the sensitivity of MRI for the diagnosis of DFO is the detection of an increased ratio of marrow region of interest (ROI)/joint fluid ROI on T2/Short Tau Inversion Recovery (STIR) sequences.[106] A systematic review and meta-analysis that compared the diagnostic accuracy of imaging tests (plain X-rays, scintigraphy, MRI, SPECT and PET) for the diagnosis of DFO showed that ^{18}F-fluorodeoxyglucose (FDG)–PET and ^{99}mTc- exametazime Hexa Methyl Propylene Amine Oxime labelled WBC scintigraphy offer the highest specificity (0.92 for both).[107] In patients with a contraindication to MRI, clinicians may choose other imaging techniques (e.g., FDG-PET/CT, HMPAO-labelled leucocyte scintigraphy or 99mTc labelled Ubiquicidin (UBI) SPECT/CT).[107–112]

Compared to nuclear (e.g., leukocyte) imaging, PET, especially combined with CT scan, offers high spatial resolution, precise anatomic localization, possibly higher sensitivity for chronic infection, easier performance, faster results, and low radiation exposure. Overall, the available studies that compared the diagnostic accuracy of MRI and nuclear imaging techniques in patients with a suspicion of DFO show conflicting results.[105,106,109,113] MRI and FDG PET/CT have several advantages compared to other anatomical and functional imaging methods, including short acquisition time, high resolution, low radiation dose, and better tolerability.[110] The availability and cost of these advanced imaging techniques may vary in different geographic locations, but they might be useful in situations when the diagnosis remains in doubt, and when there are limited options to obtain a BeBoP.

For the diagnostic accuracy of advanced imaging in DFO, the overall certainty of the evidence is moderate because of serious inconsistency, imprecision, and indirectness of results in the included studies. Although the certainty of evidence was moderate, a strong recommendation is made regarding MRI use in DFO because of the high accuracy in results, especially regarding the information on both soft tissue and bone and joint structures. Despite the certainty of evidence being moderate, a conditional rather than a strong recommendation is made regarding SPECT/CT & PET/CT use in DFO because of the lack of accessibility and feasibility of this modality and the great resources and expertise required to implement this technique.

Recommendation 10. In a person for whom there is suspicion of osteomyelitis of the foot (before or after treatment), consider obtaining bone (rather than soft tissue) samples for culture, either intraoperatively or percutaneously. (Conditional; Moderate).

Rationale. Obtaining a bone specimen to diagnose osteomyelitis is the generally accepted criterion standard for diagnosing the infection, and the only definitive way to determine the causative pathogen(s). BonE BiOPsy is, however, usually not performed in most cases of suspected DFO due to the absence of a health care professional adequately trained to perform the procedure and/or the fear of possible adverse effects, especially fracture or induced infection of the bone.[114] Published studies consistently report a low correlation between bone and non-bone culture results, most <50%, with the highest correlation for *Staphylococcus aureus*.[115–117] This is of potential importance, as incorrect identification of the bone pathogens could increase the risk of treatment failure, although this has only been reported in one published study.[118] An ongoing multicentre, prospective, randomised study (BeBoP trial) is designed to determine if treatment outcomes of DFO differ depending on the chosen diagnostic strategy, that is, a culture of bone versus one of wound.[119]

In order to provide the most accurate assessment of true pathogens, and to avoid contamination of the bone samples using the skin flora, it is important to collect a bone specimen in an aseptic manner (i.e., percutaneously via intact and uninfected skin, or intraoperatively).[115] A prospective direct comparison of 46 paired per-wound versus transcutaneous bone biopsies in patients with suspected DFO found that results were identical in only 42%.[120] To avoid a false-negative culture, some experts suggest delaying BeBoP in a patient who is receiving antibiotics until they have been off therapy for at least a few days, and ideally for at least 2 weeks. This is still a matter of debate, and the optimal duration of any antibiotic-free period before the biopsy is not known. In recent studies, a history of prior antibiotic therapy was associated with an increased likelihood of false negative bone culture.[121,122] Available published studies have established that obtaining percutaneous and intraoperative bone biopsies are both safe. Percutaneous biopsy is generally not painful (as the majority of affected patients have sensory neuropathy, and local anaesthetics can be offered), and complications are rare.[116,117] Obtaining a bone sample generally requires the services of a surgeon or radiologist, but recent studies suggest it can be performed safely at the bedside by any trained medical caregiver.[123,124] Bedside percutaneous biopsy may make it easier to obtain a bone culture when operating/imaging facilities are not feasible or available. Of note, BeBoP may not be needed if an aseptically collected specimen from a deep soft tissue infection grows only a single virulent pathogen, especially *S. aureus*.[11] Culture of bone has the advantage of determining the causative pathogen, but histology may be more sensitive if the patient is on antibiotic therapy, and more specific if the specimen contamination is a concern.

Several studies have shown one-to two-thirds of patients who undergo bone resection and from whom the surgeon obtains a sample of retained bone (variously called "marginal," "distal," or "proximal" bone) that appears clinically uninfected will have culture or pathological evidence of residual infection.[125–129] The possibility that many of the theses positive residual bone cultures are false positives is supported by the finding of a substantially lower rate of positive histology on the same specimen in two studies.[128,129] Of note, cultures may also be falsely negative, especially in patients treated with antibiotics or when samples are not appropriately transported to and processed by the microbiology laboratory. The low inter-rater agreement among pathologists on the diagnosis of osteomyelitis by histopathology[130] and the weak concordance between histopathology and culture of foot bone specimens[127] are subjects of debate.[131] This question was addressed in two more recent studies, but these also provide conflicting results.[132,133]

Since there are no available data demonstrating a clear benefit of using BeBoP results on the outcome of patients treated for a DFO, and facilities for obtaining BeBoP are not always

available, our recommendation for undertaking a BeBoP in patients with a suspicion of DFO was graded "conditional". The certainty of the evidence is moderate, based on several retrospective studies with consistency in the results regarding the diagnostic accuracy of bone cultures compared to no-bone cultures and the safety of the procedure established in these studies.

5.2 Treatment

5.2.1 Clinical question

In a person with diabetes and a soft-tissue infection of the foot, which specific antibiotic regimen (specific agent[s], route of administration, duration of therapy) should be chosen when taking into account the resolution and recurrence of infection, and the acquisition of antimicrobial resistance?

Recommendation 11. Do not treat clinically uninfected foot ulcers with systemic or local antibiotic therapy when the goal is to reduce the risk of new infection or to promote ulcer healing. Best Practice Statement.

Recommendation 12.

(a) Use any of the systemic antibiotic regimens that have been shown to be effective in published randomised controlled trials at standard (usual) dosing to treat a person with diabetes and a soft tissue infection of the foot. (Strong; High).
(b) Administer antibiotic therapy to a patient with a skin or soft tissue diabetic foot infection for a duration of 1–2 weeks. (Strong; High).
(c) Consider continuing treatment, perhaps for up to 3–4 weeks, if the infection is improving but is extensive and is resolving slower than expected or if the patient has severe PAD. (Conditional, Low).
(d) If evidence of infection has not resolved after 4 weeks of apparently appropriate therapy, re-evaluate the patient and reconsider the need for further diagnostic studies or alternative treatments. (Strong; Low).

Recommendation 13. Select an antibiotic agent for treating a DFI based on the likely or proven causative pathogen(s) and their antibiotic susceptibilities; the clinical severity of the infection; published evidence of the efficacy of the agent for infections of the diabetes-related foot; the risk of adverse events including collateral damage to the commensal flora; the likelihood of drug interactions; agent availability and costs. Best Practice Statement.

Recommendation 14. Target aerobic gram-positive pathogens only (beta-haemolytic streptococci and *Staphylococcus aureus* including methicillin-resistant strains if indicated) for people with a mild DFI, who have not recently received antibiotic therapy, and who reside in North America or Western Europe. Best Practice Statement.

Recommendation 15. Do not empirically target antibiotic therapy against *Pseudomonas aeruginosa* in cases of DFI in temperate climates, but use empirical treatment of *P. aeruginosa* if it has been isolated from cultures of the affected site within the previous few weeks, in a person with moderate or severe infection who resides in Asia or North Africa. Best Practice Statement.

Rationale. In our systematic review we could not identify data supporting the concept that prescribing antibiotic therapy for clinically uninfected ulcers either accelerates healing or reduces the risk of developing clinically apparent infection.[49] Since cultures of such open wounds will usually reveal microorganisms, including some that are commonly considered pathogens, this does not mean it is infected. As about half of all DFUs are clinically uninfected at presentation, prescribing antibiotic therapy for these could result in a substantial exposure of patients to potentially unnecessary and often harmful treatment.[134] We strongly believe that for patients with a clinically uninfected ulcer, the potential harms (to the patient, the health care system, and society as a whole) of antibiotic therapy (adverse effects of antibiotic therapy, inconvenience to the patient, cost for the drug, and likelihood of driving antibiotic resistance) outweigh any theoretical (but unproven) benefits.

Based on many studies (most limited by methodological flaws) that compared various oral or parenteral antibiotic agents in patients with DFI, treatment with any appropriately selected agent of most classes of antibiotics by either route is effective in the great majority of cases.[135–141] The choice of an antibiotic regimen should be based on the

- Likely or proven causative pathogen(s) and their antibiotic susceptibilities,
- Availability of the antibiotic,
- Published evidence of efficacy of the agent for DFIs,
- Clinical severity of the infection
- Experience of the treating team and presence of local protocols,
- Presence of patient-related factors, including a history of drug allergies, recent hospitalisation, and comorbidities such as impaired kidney function or renal dialysis,
- Likelihood of adverse events or potential drug interactions,
- Risk of collateral damage to the commensal flora,
- Costs (see our propositions for the antibiotic therapy in Table 4).

With appropriately selected antibiotic therapy (combined with any necessary surgery and proper metabolic control and wound care), most DFIs can be treated successfully with

Table 4. Proposals for the empirical antibiotic therapy according to clinical presentation and microbiological data (from Lipsky et al.[11]).[a]

Infection severity	Additional factors	Usual pathogen(s)[b]	Potential empirical regimens[c]
Mild	No complicating features	GPC	Semisynthetic penicillinase-resistant penicillin (cloxacillin)
			1st generation cephalosporin (cephalexin)
	ß-lactam allergy or intolerance	GPC	Clindamycin; fluoroquinolone (levo/moxi-floxacin); trimethoprim-sulfamethoxazole; doxycycline
	Recent antibiotic exposure	GPC + GNR	ß-lactam- ß lactamase inhibitor1 (amoxicillin/clavulanate, ampicillin/sulbactam)
			Fluoroquinolone (levo/moxi-floxacin); trimethoprim-sulfamethoxazole
	High risk for MRSA	MRSA	Linezolid; trimethoprim-sulfamethoxazole; clindamycin; doxycycline, fluoroquinolone (levofloxacin, moxifloxacin)
Moderate or severe[d]	No complicating features	GPC ± GNR	ß-lactam- ß lactamase inhibitor1 (amoxicillin/clavulanate, ampicillin/sulbactam)
			2nd, 3rd generation cephalosporine (cefuroxime, cefotaxime, ceftriaxone)
	Recent antibiotics	GPC ± GNR	ß-lactam- ß lactamase inhibitor2 (ticarcillin/clavulanate, piperacillin/tazobactam)
			2nd, 3rd generation cephalosporine (cefuroxime, cefotaxime, ceftriaxone) group 1 carbapenem (ertapenem); (depends on prior therapy; seek advice)
	Macerated ulcer or warm climate	GNR, including *Pseudomonas* sp.	ß-lactam- ß lactamase inhibitor2 (ticarcillin/clavulanate, piperacillin/tazobactam) semisynthetic penicillinase-resistant penicillin (cloxacillin) + ceftazidime or ciprofloxacin group 2 carbapenem (mero/imi-penem)
	Ischaemic limb/necrosis/ gas forming	GPC ± GNR ± strict anaerobes	ß-lactam- ß lactamase inhibitor1 (amoxicillin/clavulanate, ampicillin/sulbactam) or ß-lactam- ß lactamase inhibitor2 (ticarcillin/clavulanate, piperacillin/tazobactam)
			Group 1 (ertapenem) or 2 (mero/imi-penem) carbapenem
			2nd (cefuroxime)/3rd (cefotaxime, ceftriaxone) generation cephalosporin + clindamycin or metronidazole
	MRSA risk factors	MRSA	Consider adding, or substituting with, glycopeptides (vancomycin, teicoplanin); lILinezolid; daptomycin; fusidic acid, trimethoprim-sulfamethoxazole; doxycycline
	Risk factors for resistant GNR	ESBL	Carbapenem (erta/mero/imi-penem); fluoroquinolone (ciprofloxacin); Aminoglycoside (amikacin); colistin

Antibiotics enclosed in brackets are cited as examples. High risk for MRSA: previous MRSA infection or colonisation. MRSA risk factors: prolonged hospitalisation, intensive care admission, recent hospitalisation, recent antibiotic use, invasive procedures, HIV infection, admission to nursing homes, open wounds, haemodialysis, discharge with long-term central venous access.

Abbreviations: ESBL, extended-spectrum ß-lactamase; GNR, gram-negative rod; GPC, gram-positive cocci (staphylococci and streptococci); HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]Recommendations are based upon theoretical considerations and results of available clinical trials.

[b]Refers to isolates from an infected foot ulcer, not just colonisation at another site.

[c]Given at the usual recommended doses for serious infections. Where more than one agent is listed, only one of them should be prescribed unless otherwise indicated. Consider modifying doses or agents selected for patients with comorbidities such as azotaemia, liver dysfunction, and obesity.

[d]Oral antibiotic agents should generally not be used for severe infections, except as a follow-on (switch) after initial parenteral therapy.

limited treatment-related harms.[140–142] In case of mild infections, the most likely causative organisms are gram-positive pathogens (beta-haemolytic streptococci and *S. aureus*).[11] For these mild infections, there is also time to adjust the antibiotic therapy if cultures reveal resistant organisms or those that are not gram-positive cocci. If the infection does not resolve, therapy should be adjusted to target the bacteria cultured from the submitted specimens. Proposals for the empirical antibiotic therapy of moderate or severe DFIs are presented in Table 4. *Pseudomonas* species are less commonly isolated in studies from North America and Europe, but are more prevalent in studies from (sub)tropical climates.[136] In light of the complexity and often polymicrobial nature of DFI, definitive treatment should especially be based on principles of antibiotic stewardship: infection source control with surgery if possible; preferably starting with empiric antibiotic treatment, when appropriate, with the narrowest spectrum, shortest duration, fewest adverse effects, safest and least expensive route; and, switching to targeted (preferably oral) antibiotic therapy with agents based on the cultured pathogens.[137]

As the pathogenic versus colonising role of some bacteria identified in a wound sample, such as *Corynebacterium* sp. or coagulase-negative staphylococci, is debatable, the quality of the sample is sent to the laboratory is of utmost importance. The goal is to avoid the presence of colonisers in the sample, thereby limiting the risk of unjustifiably prescribing broad-spectrum antibiotic agents. Clinicians should consider consulting infectious diseases/microbiology expert about antibiotic therapy for difficult cases, such as those caused by unusual or highly resistant pathogens.

No antibiotic class or agent has been found to be superior to others for treating DFIs except in two studies, one of which found tigecycline to be significantly worse than ertapenem,[138] and another that found ertapenem to have a slightly lower clinical cure rate than piperacillin-tazobactam[139] Two recent retrospective studies,[140,141] and one systematic review of RCTs,[142] all confirmed our previous recommendations regarding the absence of evidence to recommend any specific antibiotic choice regarding its efficacy and the final cure of infection. In a country with a high prevalence of multi-resistant pathogens, the use of carbapenems was identified as an independent predictor of need for

major amputation, and use of vancomycin was an independent predictor of reinfection or death in one study.[143] But, as these antibiotics are often used in more severe or non-responsive cases, it is difficult to draw clear conclusions.[143]

Given the paucity of data on the resolution of infection, recurrence of infection, and the acquisition of antimicrobial resistance, our recommendation is to choose any of the systemic antibiotic regimens that have shown to be effective in published randomised controlled trials to treat a patient with diabetes and a soft tissue infection of the foot. Antibiotic dosing for skin and soft tissue infection is usually standard, but therapy for DFO may require higher doses than standard doses. We refer treating clinicians to their national guidelines for dosing advice. We suggest considering beta-lactam antibiotics (penicillins – with or without beta-lactamase inhibitors, cephalosporins, carbapenems), metronidazole (in combination with other antibiotic[s]), clindamycin, linezolid, tetracyclines, trimethoprim-sulfamethoxazole, daptomycin, fluoroquinolones, or vancomycin, but not tigecycline. Data about new combinations of beta-lactams plus beta-lactamase inhibitors, new lipoglycopeptides such as dalbavancin or oritavancin are insufficient to make any recommendation on their use in DFIs. The recommendation on how to treat patients with DFIs with these new antibiotics is conditional, based on moderate evidence.

Our systematic review did not find any new studies that justify modifying our previous recommendations about the duration of the antibiotic therapy for soft-tissue DFIs, except for post-surgical debridement of moderate or severe DFIs, for which a 10-day duration was found sufficient in a recent pilot prospective study.[144] Clinicians frequently monitor serum CRP levels during therapy for DFIs, but evidence supporting this is of low quality and based on only one study[145] Compared to our 2019 guideline, in which we advised a duration of 1–2 weeks for any soft-tissue DFIs, we make a conditional recommendation for a 10-day duration of the antibiotic therapy following a surgical debridement for moderate or severe soft tissue DFIs, with low certainty of evidence based on only one study with high risk of bias. For the other situations, we only made a best practice recommendation because of the lack of data from clinical studies on these questions. The specific aspects of the microbiology of DFIs and the potential severity of these infections are key elements that guided our recommendations. Our recommendations are in line with the general rules of the use of antimicrobial agents regarding the choice of the molecules, their way of administration and duration.[137]

5.2.2 *Clinical question*

In a person with diabetes and a bone 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?

Recommendation 16. Consider a duration of up to 3 weeks of antibiotic therapy after minor amputation for diabetes-related osteomyelitis of the foot and positive bone margin culture and 6 weeks for diabetes-related foot osteomyelitis without bone resection or amputation. (Conditional; Low).

Rationale. When prescribing antibiotic therapy for DFO, the clinician must consider several issues, in particular achieving a high enough serum level to ensure penetration to the bone. It is particularly important to consider the bioavailability of oral agents (i.e., absorption from the gastrointestinal tract into the bloodstream) if that route of therapy is selected. Penetration of antibiotic agents from the blood into the bone is variable but most classes can attain adequate levels in infected bone.[146] We suggest administering antibiotic agents at their upper recommended dosage range, and usually for a total duration of treatment (see Table 5) substantially longer than for soft-tissue infection. Prescribing long-term suppressive antibiotic therapy is generally warranted only for individuals with retained orthopaedic hardware or extensive necrotic bone that is not amenable to complete debridement.

Two randomised controlled studies suggest that the total duration of antibiotic therapy for DFO treated non-surgically does not need to be more than 6 weeks.[147,148] There are only preliminary data available that address the possibility to reduce this duration to less than 6 weeks, but this is currently under study. The duration of antibiotic therapy required for patients with DFO who undergo surgical debridement is likely to be shorter than that for patients treated non-surgically. In addition, it is unclear whether the level of amputation should play a role in deciding antibiotic duration. For instance, a patient who undergoes toe amputation without successful clinical cure can undergo another minor amputation, while a patient who undergoes total transmetatarsal amputation that fails to respond may need a below-knee amputation. In a prospective, randomized, non-inferiority, pilot trial, patients with DFO who underwent surgical debridement and received either a 3- or 6-week course of antibiotic therapy had similar outcomes and antibiotic-related adverse events.[149] As treatment with oral antibiotic regimens for residual osteomyelitis are associated with failure rates similar to those with intravenous regimens, this may help reduce the length of hospital stay in those patients.[150] The recommendation about the duration and administration of post-surgical antibiotic therapy is conditional with a low certainty of evidence, based on a few studies with high risk of bias.

Recommendation 17. Use the outcome at a minimum follow-up duration of 6 months after the end of the antibiotic therapy to

Table 5. Duration of antibiotic therapy according to the clinical situation.

	Route	Duration
Infection severity (skin and soft tissues)		
Class 2: Mild	Oral	1–2 weeks[a]
Class 3/4: Moderate/severe	Oral/initially iv	2–4 weeks
Bone/joint		
Resected	Oral/initially iv	2–5 days
Debrided (soft tissue infection)	Oral/initially iv	1–2 weeks
Positive culture or histology of bone margins after bone resection	Oral/initially iv	3 weeks
No surgery or dead bone	Oral/initially iv	6 weeks

Abbreviation: iv, intravenous.

[a]10 days following surgical debridement.

diagnose remission of diabetes-related osteomyelitis of the foot. Best Practice Statement.

Rationale. It may be difficult to know when DFO has been successfully treated. For a chronic infection that resolves slowly, and frequently recurs if not adequately treated, we initially prefer using the term remission to cure. This is defined as the absence of any persistent or new episode of DFO at the initial or contiguous site, but the delay for which a remission should be assessed is uncertain.

In patients with DFO, there are often few clinical signs and symptoms to follow, although the resolution of any overlying soft tissue infection is reassuring. A decrease in previously elevated serum inflammatory markers suggests improving infection. Plain X-rays showing no further bone destruction and better yet signs of bone healing also suggest improvement. Some of the newer advanced imaging studies, for example, WBC-labelled SPECT/CT and FDG PET/CT, may be more sensitive in assessing the resolution of infection. Long-term (typically at least a year) follow-up is classically recommended before declaring the infection cured. Of note, if the underlying conditions that predisposed the patient to the index episode of DFO are not adequately addressed (e.g., pressure off-loading, surgery to correct foot deformity), another infection at the same site may be a new recurrence rather than a relapse. We think that using an overly long post-treatment period to define remission may result in calling a new episode of DFO associated with a new DFU, thus overestimating the risk of relapse in these cases. Therefore, we suggest using a minimum follow-up duration of 6 months after the end of the antibiotic therapy to define the remission of a DFO. In addition, life-long frequent foot examinations in this population are warranted since most patients with a history of DFI are at high risk of future foot complications.[20]

5.2.3 Clinical question

In a person with diabetes and moderate or severe infection of the foot, including osteomyelitis, 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)?

Recommendation 18. The urgent surgical consultation should be obtained in cases of severe infection or moderate DFI complicated by extensive gangrene, necrotising infection, signs suggesting deep (below the fascia) abscess, compartment syndrome, or severe lower limb ischaemia. Best Practice Recommendation.

Recommendation 19. Consider performing early (within 24–48 h) surgery combined with antibiotics for moderate and severe DFIs to remove the infected and necrotic tissue. (Conditional; Low).

Recommendation 20. In people with diabetes, PAD and a foot ulcer or gangrene with infection involving any portion of the foot obtain an urgent consultation by a surgical specialist as well as a vascular specialist in order to determine the indications and timings of drainage and/or revascularisation procedure. Best Practice Statement.

Rationale. Retrospective studies comparing early surgery (variously defined, but usually within 72 h of presentation) versus delayed surgery (3–6 days after admission) in hospitalised patients with a severe, deep DFI, with or without osteomyelitis have reported lower rates of major lower extremity amputation and higher rates of wound healing.[151–153] Similarly, patients with moderate or severe DFIs who had a delayed admission at specialised foot centres were more likely to require major amputation.[154] We think that surgical therapy should always be at least considered in cases of severe DFI, and in other cases for which non-surgical treatment is likely to fail. For such an evaluation, consultation by a surgical specialist is essential; therefore, we formulated a Best Practice Statement. Severe DFIs include those described in the background section of the present paper. Current guidelines on PAD associated

with diabetes-related foot highlight that the combination of infection plus PAD portents a poor clinical outcome if both are not treated adequately.[7] Therefore, in case of infection, the patient should be assessed for the presence and severity of PAD. As clinical assessment is often unreliable, it is important to also perform non-invasive tests, for example, Doppler waveform analysis combined with ankle pressure measurement, as well as toe pressure measurements.[7] Based on the assessment of the wound and the amount of tissue loss, the results of non-invasive tests, and the IWGDF/IDSA infection severity score, all patients should be classified according to the WIfI classification scheme,[9] which helps to further determine the need for a vascular intervention as described in the IWGDF PAD guidelines.[7]

Recommendation 21. Consider performing surgical resection of infected bone combined with systemic antibiotics in a person with diabetes-related osteomyelitis of the foot. (Conditional; Low).

Recommendation 22. Consider antibiotic treatment without surgery in case of (i) forefoot osteomyelitis without an immediate need for incision and drainage to control infection, (ii) without PAD, and (iii) without exposed bone. (Conditional; Low).

Rationale. Surgical resection of infected bone has long been the standard treatment of osteomyelitis, but over the past 2 decades, evidence from several retrospective case series,[155–157] retrospective cohort studies,[158–160] and one prospective controlled study[161] have demonstrated that in properly selected patients mostly with forefoot DFO, antibiotic therapy alone is as effective as surgery regarding the remission of DFO and need for amputation. This suggestion is largely based on studies that have generally not stratified patients with DFO based on the presence or severity of any concomitant soft tissue infection.[162] The studies that have addressed this issue have generally found that patients with DFO who had concomitant soft tissue infection (and perhaps those with PAD) required more urgent and extensive surgery, had longer lengths of stay, and had worse outcomes.[163]

The subjects in most studies, specifically in the RCT, were excluded if they obviously needed surgery (e.g., exposed bone, compartment syndrome, undrained abscess) and did not have PAD. If perfusion is severely compromised, revascularisation should always be performed (either before or after any soft tissue/bone resection). In a subsequently well-perfused foot, the treatment of the DFI should not be different. The dilemma will be how to treat a patient with DFO with limited soft tissue infection, seemingly mild ischaemia, and no indication for drainage. Given the unreliability of any vascular assessment, there is a clear risk that the perfusion deficit may be underestimated, and any operation could result in a non-healing wound. One small study suggests that patients with a concomitant acute soft-tissue infection and osteomyelitis of the foot not requiring urgent surgical debridement can be treated using a two-step approach consisting firstly of antibiotic therapy for the soft-tissue infection, and secondly, after a free-antibiotic period, bone culture-guided antibiotics for treatment of DFO.[164] Overall, there is inconsistency in results of studies that compared surgical versus medical approaches for DFO between the RCT and the cohort studies, and a high risk of bias (in the cohort studies). The results seem, however, to have no serious imprecision. Compared to the previous guideline, in which strong recommendations were made regarding the indications for predominantly medical versus surgical approaches for DFO, we classified the strength of the recommendation as conditional due to the low certainty of the evidence of the available data.

5.2.4 Clinical question

In a person with diabetes and a foot infection, does the addition of any specific adjunctive or topical antibiotic treatment to systemic antibiotic therapy and surgery improve the outcome of infection?

Recommendation 23. We suggest not using the following treatments to address DFIs: (a) adjunctive G-CSF treatment or (b) topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative-pressure wound therapy (with or without instillation). Conditional; Low.

Rationale. According to systematic reviews,[49,114] adding G-CSF to a diabetes-related foot treatment does not significantly affect the likelihood of resolution of infection, healing of the wound, or the duration of systemic antibiotic therapy. It does seem to be associated with a reduced likelihood of lower extremity surgical interventions (including amputation) and a reduced duration of hospital stay, although the profile of patients who might benefit is unclear, especially in relation to the costs and potential adverse effects.

Various types of topical antiseptics have been used to treat DFUs, but the available evidence does not support any beneficial effect for most of them.[165] Silver has been shown to have an antibacterial effect, and topical silver-containing treatments (creams, dressings, etc.) are widely used for IDFUs. Silver compounds do not offer benefits in ulcer healing (as described in the IWGDF wound healing guidelines[8]) and there is no evidence to support their effectiveness in the treatment of the infectious aspects of a DFU. Topical administration of other agents only seems to have a marginal effect on the outcomes of these infections in low-quality studies.[49]

Recommendation 24. We suggest not using topical (sponge, cream, and cement) antibiotics in combination with systemic

antibiotics for treating either soft-tissue infections or osteomyelitis of the foot in patients with diabetes. (Conditional; Low).

Rationale. Treatment with topical antimicrobial therapy has many theoretical advantages, particularly requiring only a small dose directly at the site of infection, thus potentially limiting issues of cost, adverse events, and antibiotic resistance. The potential advantage of topical versus systemic antibiotic therapy is to deliver very high concentrations of antibiotics at the site of infection that could not be achieved using the systemic route of administration. Another potential advantage is to limit potential collateral damage to gut microflora, including the emergence of multiresistant bacteria and *Clostridioides* difficile-associated diarrhoea.

Studies that have addressed the potential benefit of topical administration of antibiotics as adjunctive treatment to systemic antibiotic therapy for soft-tissue DFIs have provided conflicting results.[165–171] Limited data from studies with high-risk of bias suggest a potential benefit of antibiotic-loaded cement and intraoperative site vancomycin powder application in patients with DFO treated by surgical debridement.[172–175] Overall, these studies, characterised by a potentially high risk of bias, inconsistency, imprecision and low certainty, do not demonstrate a significant clinical benefit of topical antibiotics in the treatment of either diabetes-related foot soft tissue or bone infections. There is also insufficient evidence on whether adjunctive agents meaningfully affect clinical outcome and the safety of routinely using local antibiotics has not yet been clearly established. Therefore, we elected to suggest against the use of topical antibiotics. Future studies should apply learnings from prior studies to ensure statistically robust and clinically useful RCTs.

Recommendation 25. We suggest not using HBO therapy or topical oxygen therapy as an adjunctive treatment for the sole indication of treating a DFI. (Conditional; Low).

Rationale. Hyperbaric oxygen therapy is often used in an attempt to improve DFU healing, but there are few data on its potential role in controlling infection. The results of one RCT suggested that the use of HBO treatment led to fewer positive wound cultures after treatment, but the study's high risk of bias (small study size, poor quality, non-standardised methods, and non-standardized definitions used) and indirectness of the evidence do not offer support for the use of systemic HBO in DFI.[49] We found no studies on using topical HBO for infection upon which to base a recommendation. Equity and feasibility are limited due to high costs and low availability of HBO therapy. In the absence of any substantial data to support its effect in treating either soft tissue or bone infection or in accelerating ulcer healing via an antimicrobial effect, we think the costs and inconvenience outweigh any theoretical benefits. The recommendation against the use of HBO therapy for DFIs is conditional given the absence of compelling data on its efficacy, based on low certainty of evidence.

Areas with absent or inconsistent evidence. Bioactive glass compounds have been used topically as an adjunctive treatment in surgical cases of DFO, but the insufficient data available prevent us from providing a recommendation on this therapeutic approach.[176,177] Current treatment guidelines do not endorse any specific antibiotic agent for diabetes-related osteomyelitis of the foot, but our systematic review identified two retrospective studies that suggest the addition of rifampicin to combination antimicrobial regimen results in improved cure rates for osteomyelitis.[118,178] The certainty of the evidence is low, based on the inconsistency of outcomes. The potential of drug-related adverse events and the risk of drug-drug interactions, especially in aged patients usually treated with other medications, justify obtaining valid data on its potential benefit before considering its routine use.

6 KEY CONTROVERSIES

Some areas concerning the management of DFIs still need further development. The following questions are those we found of most interest:

- How and when to determine whether an infection, including soft-tissue and osteomyelitis, has resolved?
- What are the most useful serum biomarkers to help determine whether a DFU is infected and if underlying osteomyelitis is present, especially when clinical and imaging assessments are inconclusive?
- To what extent can the currently recommended durations of antibiotic therapy be reduced for soft-tissue and osteomyelitis?
- When, and which, available advanced imaging studies should clinicians order in a patient with a DFI?
- Does using information from a BeBoP, including at the amputation site, improve outcomes of DFO?
- What is the place of various new antibiotics in the management of DFIs?
- Is there a definition for, and practical clinical use of, the concept of chronic biofilm infection of a DFU?
- Does molecular (genotypic) microbiological testing for DFI help guide antimicrobial therapy and improve outcomes?
- What is the potential of the topical administration of antimicrobials to limit the use of systemic antibiotics in DFIs?

Notes

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and quality of the papers selected for the analysis, and the review of the final document.

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Disclaimer. The guideline working group is committed to developing trustworthy clinical practice guidelines through transparency and full disclosure by those participating in the process of guideline development. In order to prevent a major Conflict of Interest (COI), members of the guideline group were not allowed to serve as an officer, board member, trustee, owner, or employee of a company directly or indirectly involved in the topic of this guideline. Before the first and last meeting of the guideline working group, members were asked to report any COI in writing. In addition, at the beginning of each meeting, this question was also asked and if answered yes, the members were asked to submit a COI form. These COIs included income received from biomedical companies, device manufacturers, pharmaceutical companies, or other companies producing products related to the field. In addition, industry relationships had to be disclosed each time and these included ownerships of stocks/options or bonds of a company, any consultancy, scientific advisory committee membership, or lecturer for a company, research grants, and income from patents. These incomes could either be personal or obtained by an institution with which the member had a relationship. All disclosures were reviewed by the chair and secretary of the working groups and can be found at https://iwgdfguidelines.org/about-iwgdf-guidelines/biographies/. No company was involved in the development or review of the guidelines. Nobody involved in the guideline development received any payment or remuneration of any costs, except for travel and accommodation expenses when meeting on-site.

Working group members were additionally requested to declare COI and refrain from the risk of bias scoring process or voting process for particular interventions if they had a professional working relationship with any of the co-authors on a particular paper.

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