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SUPPLEMENT ARTICLE

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Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update)

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Abstract

The International Working Group on the Diabetic Foot (IWGDF) has published evidence-based guidelines on the prevention and management of diabetic foot disease since 1999. This guideline is on the diagnosis and treatment of foot infection in persons with diabetes and updates the 2015 IWGDF infection guideline. On the basis of patient, intervention, comparison, outcomes (PICOs) developed by the infection committee, in conjunction with internal and external reviewers and consultants, and on systematic reviews the committee conducted on the diagnosis of infection (new) and treatment of infection (updated from 2015), we offer 27 recommendations. These cover various aspects of diagnosing soft tissue and bone infection, including the classification scheme for diagnosing infection and its severity. Of note, we have updated this scheme for the first time since we developed it 15 years ago. We also review the microbiology of diabetic foot infections, including how to collect samples and to process them to identify causative pathogens. Finally, we discuss the approach to treating diabetic foot infections, including selecting appropriate empiric and definitive antimicrobial therapy for soft tissue and for bone infections, when and how to

International Working Group on the Diabetic Foot (IWGDF); http://www.iwgdfguidelines.org

approach surgical treatment, and which adjunctive treatments we think are or are not useful for the infectious aspects of diabetic foot problems. For this version of the guideline, we also updated four tables and one figure from the 2015 guideline. We think that following the principles of diagnosing and treating diabetic foot infections outlined in this guideline can help clinicians to provide better care for these patients.

KEYWORDS

diabetic foot, diagnosis, foot ulcer, guidelines, infection, microbiology, osteomyelitis

LIST OF RECOMMENDATIONS

1. (a) Diagnose a soft tissue diabetic foot infection clinically, based on the presence of local or systemic signs and symptoms of inflammation. (Strong; low)
   (b) Assess the severity of any diabetic foot infection using the Infectious Diseases Society of America/International Working Group on the Diabetic Foot classification scheme. (Strong, moderate)
2. Consider hospitalizing all persons with diabetes and a severe foot infection and those with a moderate infection that is complex or associated with key relevant morbidities. (Strong; low)
3. In a person with diabetes and a possible foot infection for whom the clinical examination is equivocal or uninterpretable, consider ordering an inflammatory serum biomarker, such as C-reactive protein, erythrocyte sedimentation rate, and perhaps procalcitonin, as an adjunctive measure for establishing the diagnosis. (Weak; low)
4. As neither electronically measuring foot temperature nor using quantitative microbial analysis has been demonstrated to be useful as a method for diagnosing diabetic foot infection, we suggest not using them. (Weak; low)
5. In a person with diabetes and suspected osteomyelitis of the foot, we recommend using a combination of the probe-to-bone test, the erythrocyte sedimentation rate (or C-reactive protein and/or procalcitonin), and plain X-rays as the initial studies to diagnose osteomyelitis. (Strong; moderate)
6. (a) In a person with diabetes and suspected osteomyelitis of the foot, if a plain X-ray and clinical and laboratory findings are most compatible with osteomyelitis, we recommend no further imaging of the foot to establish the diagnosis. (Strong; low)
   (b) If the diagnosis of osteomyelitis remains in doubt, consider ordering an advanced imaging study, such as magnetic resonance imaging scan, ^{18}F-FDG-positron emission tomography/computed tomography (CT) or leukocyte scintigraphy (with or without CT). (Strong; moderate)
7. In a person with diabetes and suspected osteomyelitis of the foot, in whom making a definitive diagnosis or determining the causative pathogen is necessary for selecting treatment, collect a sample of bone (percutaneously or surgically) to culture clinically relevant bone microorganisms and for histopathology (if possible). (Strong; low)
8. (a) Collect an appropriate specimen for culture for almost all clinically infected wounds to determine the causative pathogens. (Strong; low)
   (b) For a soft tissue diabetic foot infection, obtain a sample for culture by aseptically collecting a tissue specimen (by curettage or biopsy) from the ulcer. (Strong; moderate)
9. Do not use molecular microbiology techniques (instead of conventional culture) for the first-line identification of pathogens from samples in a patient with a diabetic foot infection. (Strong; low)
10. Treat a person with a diabetic foot infection with an antibiotic agent that has been shown to be effective in a published randomized controlled trial and is appropriate for the individual patient. Some agents to consider include penicillins, cephalosporins, carbapenems, metronidazole (in combination with other antibiotic[s]), clindamycin, linezolid, daptomycin, fluoroquinolones, or vancomycin, but not tigecycline. (Strong; high)
11. Select an antibiotic agent for treating a diabetic foot infection based on: the likely or proven causative pathogen(s) and their antibiotic susceptibilities; the clinical severity of the infection; published evidence of efficacy of the agent for diabetic foot infections; risk of adverse events, including collateral damage to the commensal flora; likelihood of drug interactions; agent availability; and, financial costs. (Strong; moderate)
12. Administer antibiotic therapy initially by the parenteral route to any patient with a *severe* diabetic foot infection. Switch to oral therapy if the patient is clinically improving and has no contraindications to oral therapy and if there is an appropriate oral agent available. (Strong; low)
13. Treat patients with a mild diabetic foot infection, and most with a moderate diabetic foot infection, with oral antibiotic therapy, either at presentation or when clearly improving with initial intravenous therapy. (Weak; low)
14. We suggest not using any currently available topical antimicrobial agent for treating a mild diabetic foot infection. (Weak; moderate)
15. (a) Administer antibiotic therapy to a patient with a skin or soft tissue diabetic foot infection for a duration of 1 to 2 weeks. (Strong; high)

(b) Consider continuing treatment, perhaps for up to 3 to 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. (Weak; low)

(c) 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)

16. For patients who have not recently received antibiotic therapy and who reside in a temperate climate area, target empiric antibiotic therapy at just aerobic gram-positive pathogens (beta-haemolytic streptococci and *Staphylococcus aureus*) in cases of a *mild* diabetic foot infection. (Strong; low)
17. For patients residing in a tropical/subtropical climate, or who have been treated with antibiotic therapy within a few weeks, have a severely ischemic affected limb, or a moderate or severe infection, we suggest selecting an empiric antibiotic regimen that covers gram-positive pathogens, commonly isolated gram-negative pathogens, and possibly obligate anaerobes in cases of moderate to severe diabetic foot infections. Then, reconsider the antibiotic regimen based on both the clinical response and culture and sensitivity results. (Weak; low)
18. Empiric treatment aimed at *Pseudomonas aeruginosa* is not usually necessary in temperate climates, but consider it if *P aeruginosa* has been isolated from cultures of the affected site within the previous few weeks, or in tropical/subtropical climates (at least for moderate or severe infection). (Weak; low)
19. Do not treat clinically uninfected foot ulcers with systemic or local antibiotic therapy with the goal of reducing the risk of infection or promoting ulcer healing. (Strong; low)
20. Nonsurgeons should urgently consult with a surgical specialist in cases of severe infection or of moderate infection complicated by extensive gangrene, necrotizing infection, signs suggesting deep (below the fascia) abscess or compartment syndrome, or severe lower limb ischemia. (Strong; low)
21. (a) In a patient with diabetes and uncomplicated forefoot osteomyelitis, for whom there is no other indication for surgical treatment, consider treating with antibiotic therapy without surgical resection of bone. (Strong; moderate)

    (b) In a patient with probable diabetic foot osteomyelitis with concomitant soft tissue infection, urgently evaluate for the need for surgery as well as intensive post-operative medical and surgical follow-up. (Strong; moderate)
22. Select antibiotic agents for treating diabetic foot osteomyelitis from among those that have demonstrated efficacy for osteomyelitis in clinical studies. (Strong; low)
23. (a) Treat diabetic foot osteomyelitis with antibiotic therapy for no longer than 6 weeks. If the infection does not clinically improve within the first 2 to 4 weeks, reconsider the need for collecting a bone specimen for culture, undertaking surgical resection, or selecting an alternative antibiotic regimen. (Strong; moderate)

    (b) Treat diabetic foot osteomyelitis with antibiotic therapy for just a few days if there is no soft tissue infection and all the infected bone has been surgically removed. (Weak; low)
24. For diabetic foot osteomyelitis cases that initially require parenteral therapy, consider switching to an oral antibiotic regimen that has high bioavailability after perhaps 5 to 7 days, if the likely or proven pathogens are susceptible to an available oral agent and the patient has no clinical condition precluding oral therapy. (Weak; moderate)
25. (a) During surgery to resect bone for diabetic foot osteomyelitis, consider obtaining a specimen of bone for culture (and, if possible, histopathology) at the stump of the resected bone to identify if there is residual bone infection. (Weak; moderate)

    (b) If an aseptically collected culture specimen obtained during the surgery grows pathogen(s), or if the histology demonstrates osteomyelitis, administer appropriate antibiotic therapy for up to 6 weeks. (Strong; moderate)
26. For a diabetic foot infection, do not use hyperbaric oxygen therapy or topical oxygen therapy as an adjunctive treatment if the only indication is specifically for treating the infection. (Weak; low)
27. To specifically address infection in a diabetic foot ulcer:

    (a) do not use adjunctive granulocyte colony stimulating factor treatment (Weak; moderate), and

    (b) do not routinely use topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative pressure wound therapy (with or without instillation). (Weak; low)

1 | INTRODUCTION

The prevalence of diabetes continues to increase worldwide, leading to a rising incidence of foot complications, including infections.[1] Diabetic foot infections (DFIs) are associated with substantial morbidities, requiring frequent health care provider visits, daily wound care, antimicrobial therapy, surgical procedures, and high health care costs.[2,3] Of particular importance, DFIs remain the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputation.[4-6] Outcomes in patients presenting with an infected diabetic foot ulcer (IDFU) are poor: 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] Thus, it is not surprising that a bibliographic analysis of global research on DFUs in the past 10 years found that infection (DFI) scored among the most frequent topics and the most highly cited publications.[7]

Managing DFIs requires careful attention to properly diagnosing the condition, obtaining appropriate specimens for culture, thoughtfully selecting antimicrobial therapy, and quickly determining when surgical interventions are required and providing any needed additional wound and overall patient care. A systematic,

evidence-based approach to managing DFIs likely improves outcomes, specifically resolution of infection, and helps avoid complications, such as lower extremity amputation. This is best delivered by interdisciplinary teams, which should include among the membership, whenever possible, an infectious diseases or clinical/medical microbiology specialist.[8] This team should, of course, also attempt to ensure optimal local wound care (eg, cleansing and debridement), pressure off-loading, vascular assessment and treatment if needed, and metabolic (particularly glycaemic) control.

Several guidelines are available to assist clinicians in managing DFIs. A panel of infectious diseases experts convened by the International Working Group on the Diabetic Foot (IWGDF) has published widely used guideline documents quadrennially since 2004.[9] This current guideline updates both the format and content of the most recent previous guideline, published in 2016.[9] Specifically, it incorporates information from the concurrently published systematic reviews of the literature developed by the infection committee: an update of the 2016 systematic review on interventions in the management of infection in the diabetic foot[10] and a newly conducted review of issues related to diagnosis of DFIs. Of note, we have slightly modified the classification system for defining the presence and severity of an infection of the foot in a person with diabetes (see Table 1) that the IWGDF and the Infectious Diseases Society of America (IDSA) first developed in 2004.[11,12] In this guideline, we have broadly divided our recommendations into those related to diagnosis, microbiological assessment, and treatment (antibiotic, surgical, and adjunctive).

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

Clinical classification of infection, with definitions	IWGDF classification
Uninfected:	
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 cm[a] around the wound • Local tenderness or pain • Local increased warmth • Purulent discharge And no other cause(s) of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, or venous stasis)	
- Infection with no systemic manifestations (see below) involving • only the skin or subcutaneous tissue (not any deeper tissues), and • any erythema present does not extend >2 cm[b] around the wound	2 (mild infection)
- Infection with no systemic manifestations and involving • erythema extending ≥2 cm[a] from the wound margin, *and/or* • tissue deeper than skin and subcutaneous tissues (eg, tendon, muscle, joint, and bone,)	3 (moderate infection)
- 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 $PaCO_2$ < 4.3 kPa (32 mmHg) • White blood cell count >12 000/mm^3, or <4000/mm^3, or >10% immature (band) forms	4 (severe infection)
- Infection involving bone (osteomyelitis)	Add "(O)" after 3 or 4[c]

[a]Infection refers to any part of the foot, not just of a wound or an ulcer.
[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).
The presence of clinically significant foot ischaemia makes both diagnosis and treatment of infection considerably more difficult.

2 | BACKGROUND

Infection is best defined as an invasion and multiplication of microorganisms in host tissues that induces a host inflammatory response, usually followed by tissue destruction. Almost all DFIs occur in open wounds; as these are colonized with microorganisms, infection cannot be defined using only the results of wound cultures. Instead, DFI is defined clinically as the presence of manifestations of an inflammatory process in any tissue below the malleoli in a person with diabetes mellitus. In persons with diabetic foot complications, signs and symptoms of inflammation may, however, be masked by the presence of peripheral neuropathy, or peripheral artery disease or immune dysfunction. DFIs usually begin with a break in the protective cutaneous envelope, typically in a site of trauma or ulceration, most often in a person with peripheral neuropathy and frequently with peripheral artery disease.[13] While rarely the primary cause of foot ulcers, the presence of limb ischemia increases the risk of an ulcer becoming infected[4,14-16] and adversely affects the outcome of infection.[4,17,18] Foot ulcers in persons with diabetes often become chronic, related to increased biomechanical stress, hyperglycaemia and its metabolic consequences, persistent inflammation, apoptosis, or ischaemia.[19,20] Factors that predispose to foot infection include having an ulcer that is deep, long-standing or recurrent, or of traumatic aetiology; ill-defined diabetes-related immunological perturbations, particularly with neutrophil dysfunction; or, chronic renal failure.[14,16,21-24] Although examined in only a few studies, a history of chronic hyperglycaemia may predispose to DFIs, and its presence at presentation may suggest a rapidly progressive or destructive (necrotising) infection.[25,26]

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 proximal spread of infection.[27] The inflammatory response induced by infection may cause compartmental pressure to exceed capillary pressure, leading to ischaemic tissue necrosis and thereby progressive infection.[28,29] The tendons within the compartments facilitate 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.[30,31]

Systemic symptoms (eg, feverishness and 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.[4,32,33] If not diagnosed and properly treated, DFIs tend to progress, sometimes rapidly.[34] Thus, an experienced consultant (or team) should optimally evaluate a patient with a severe DFI within 24 hours.[35] Accumulations of purulent secretions, especially if under pressure or associated with necrosis, require prompt (usually within 24 hours) decompression and drainage. Although bone resection (preferably limited, avoiding amputation) is often useful for treating osteomyelitis, it is usually soft tissue infection that requires urgent antimicrobial therapy and surgical intervention.

The aim of this document is to provide 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.

3 | METHODS

In this guideline, we have followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, which is structured around clinical questions in the patient-intervention-comparison-outcome (PICO) format, systematic literature searches, and assessment of the available evidence, followed by developing recommendations and their rationale.[36,37]

First, a multidisciplinary working group of independent experts (the authors of this guideline) was installed by the IWGDF editorial board. The members of the working group devised the clinical questions, which they revised after consultation with external experts from various geographical regions and the IWGDF Editorial Board. The aim was to ensure the relevance of the questions for clinicians and other health care professionals in providing useful information on the management of foot infections in persons with diabetes. We also formulated what we considered critically important outcomes relevant for daily care, using the set of outcomes defined by Jeffcoate et al[38] as a reference guide.

Second, we systematically reviewed the literature to address the agreed upon clinical questions. For each assessable outcome, we graded the quality of evidence based on the risk of bias of included studies, effect sizes, presence of inconsistency, and evidence of publication bias (the latter where appropriate). We then rated the quality of evidence as "high," "moderate," or "low." The systematic reviews supporting this guideline are published separately.[39,40]

Third, we formulated recommendations to address each clinical question. We aimed to be clear, specific, and unambiguous on what we recommend, for which persons, and under what circumstances. Using the GRADE system, we provided the rationale for how we arrived at each recommendation, based on the evidence from our systematic reviews,[39,40] expert opinion where evidence was not available, and a careful weighing of the benefits and harms, patient preferences, and financial costs (resource utilization) related to the intervention or diagnostic method.[36,37] On the basis of these factors, we graded the strength of each recommendation as "strong" or "weak," and for or against a particular intervention or diagnostic method. All our recommendations (with their rationales) were reviewed by the same international experts who reviewed the clinical questions, as well as by the members of the IWGDF Editorial Board.

We refer those seeking a more detailed description on the methods for developing and writing these guidelines to the "IWGDF Guidelines development and methodology" document.[41]

4 | DIAGNOSIS

PICO 1a:

In a person with diabetes and a foot infection, do increasing levels of severity of the IWGDF/IDSA criteria correlate with increasing rates of adverse outcomes (eg, need for hospitalisation, failure to resolve infection, or lower extremity amputation)?

Recommendation 1:

a) Diagnose a soft tissue DFI clinically, based on the presence of local or systemic signs and symptoms of inflammation. (Strong; low)
b) Assess the severity of any DFI using the IDSA/IWGDF classification scheme. (Strong, Moderate).

Rationale:

The clinician seeing a patient with a DFU should always assess for the presence of an infection and, if present, classify the infection's severity. Experts have proposed many classification schemes for DFU (see IWGDF Guideline on classification in this issue), many of which only include the presence or absence of "infection" (which is rarely specifically defined), but in the past decade, most authorities have recommended using the IWGDF/IDSA classification that was first published in 2004. Two prospective cohort studies have validated all or part of the IWGDF/IDSA DFI classification, and one prospective and four retrospective cohort studies have validated the IWGDF/IDSA as part of a larger diabetic foot classification system. These and other studies from around the world have provided some evidence that increasing severity of infection is associated with higher levels of inflammatory markers,[42] a greater likelihood of the patient being hospitalised for treatment, longer duration of hospital stay, greater

likelihood and higher level of lower extremity amputation, and higher rate of readmission.[4,33,43,44] Sepsis is uncommonly reported (perhaps partly being unrecognized) in patients with a DFI, even in the presence of extensive local signs and symptoms of infection. Thus, we considered whether we should replace using the findings of the systemic inflammatory response syndrome (SIRS) by another classification for severe infection, eg, National Early Warning Score (NEWS)[45,46] or quick sequential organ failure assessment (qSOFA).[47] These were, however, developed for identification or prediction of outcomes in patients with sepsis, and there are no data to support changing from using SIRS to other classifications for DFIs.

Two commonly used classifications for DFUs, Wound, Ischemia, and foot Infection (WIfI) and Site, Ischaemia, Neuropathy, Bacterial Infection, and Depth (SINBAD), which use the IWGDF/IDSA classification for the infection component, have been validated with patient data.[48,49] The IWGDF/IDSA classification has several advantages, including having the most studies to validate its use in different populations. It is relatively easy for the clinician to use, requiring only a clinical examination and standard blood and imaging tests, helps direct diagnostic and therapeutic decisions about infection, is associated with no obvious harms, and has been widely accepted by the academic community and practicing clinicians. Furthermore, other available classification schemes were not specifically developed or validated for DFIs.[50]

For the current guideline, we have made a *clarification* in the infection classification scheme (Table 1). We define infection based on the presence of evidence of (a) inflammation of any part of the foot, not just an ulcer or wound, or (b) findings of SIRS. We have also made one *change* in the classification scheme. Because of the important diagnostic, therapeutic, and prognostic implications of osteomyelitis, we now separate it out by indicating the presence of bone infection with "(O)" after the grade number (3 or 4) (see Table 1). Although uncommon, bone infection may be documented in the absence of local inflammatory findings. In this case, the foot should be classified as infected (either grade 3/moderate if there are no SIRS findings or 4/severe if there are), with an (O). As the presence of osteomyelitis means the foot is infected, it cannot be grade 1/uninfected, and because the infection is subcutaneous, it cannot be grade 2/mild. As the grade 3/moderate classification is the largest and most heterogeneous group, we considered dividing it into subgroups of just lateral spread (≥2 cm from the wound margin) or just vertical spread (deeper than the subcutaneous tissue). We discarded this idea as it would add to the complexity of the diagnostic scheme, especially with our decision to add the (O) for osteomyelitis.

PICO 1b:

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

Recommendation 2:

Consider hospitalising all persons with diabetes and a severe foot infection and those with a moderate infection that is complex or associated with key relevant morbidities. (Strong; low)

Rationale:

Hospitalisation is an expensive and finite resource and may subject the patient to some inconvenience and potential nosocomial risks. But while many patients with a DFI do not need to be hospitalised, some certainly should be. Possible reasons to hospitalise a person with diabetes who presents with a more complex foot infection include more intensive assessment for progression of local and systemic conditions; expediting obtaining diagnostic procedures (such as advanced imaging or vascular assessment); administering parenteral antibiotic therapy and fluid resuscitation; correcting metabolic and cardiovascular disturbances; and, more rapidly accessing needed specialty (especially surgical) consultation. Limited evidence suggests that monitoring and correcting severe hyperglycaemia may be beneficial.[26] Patients with a complex infection, such as those needing urgent surgery (eg, because of extensive gangrene, deep abscess, or compartment syndrome), having selected comorbidities (eg, severe peripheral artery disease, renal failure, and immunocompromised state) or having social, physical, or psychological vulnerabilities, may also benefit from (or even require) hospitalization (see Table 2). The presence of bone infection does not necessarily require hospitalization unless there is substantial associated soft tissue infection, for diagnostic testing or for surgical treatment. Fortunately, almost all patents with a mild infection, and many with a moderate infection, can be treated in an ambulatory setting. Most published studies of DFIs have enrolled hospitalized patients, but over the past two decades, several have reported good results with outpatient treatment.[51-53] The IDSA/IWGDF classification scheme was not designed to help determine when an infection has *resolved* (ie, the absence of signs and symptoms that were used to diagnose infection), but it makes sense that it could be used this way and has been in some studies of antibiotic therapy for DFIs.

PICO 2a:

In a person with diabetes and a suspected foot infection, how well do the IWGDF/IDSA clinical criteria for diagnosing soft tissue infection correlate with other diagnostic tests?

Recommendation 3:

In a person with diabetes and a possible foot infection for whom the clinical examination is equivocal or uninterpretable, consider ordering an inflammatory serum biomarker, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and perhaps procalcitonin (PCT), as an adjunctive measure for establishing the diagnosis. (Weak; low)

Rationale:

There are several diagnostic methods against which clinical examinations could be compared to evaluate their ability to assess the

TABLE 2 Characteristics suggesting a more serious diabetic foot infection and potential indications for hospitalization

A. Findings suggesting a more serious diabetic foot infection	
Wound specific	
Wound	Penetrates to subcutaneous tissues (eg, 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, discoloration, necrosis or gangrene, ecchymoses or petechiae, and new anaesthesia or localised pain
General	
Presentation	Acute onset/worsening or rapidly progressive
Systemic signs	Fever, chills, hypotension, confusion, and volume depletion
Laboratory tests	Leucocytosis, highly elevated C-reactive protein or erythrocyte sedimentation rate, severe or worsening hyperglycaemia, acidosis, new/worsening azotaemia, and electrolyte abnormalities
Complicating features	Presence of a foreign body (accidentally or surgically implanted), puncture wound, deep abscess, arterial or venous insufficiency, lymphedema, immunosuppressive illness or treatment, acute kidney injury
Failing treatment	Progression while on apparently appropriate antibiotic and supportive therapy
B. Some Factors suggesting hospitalisation may be necessary	
Severe infection (see findings suggesting a more serious diabetic 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	
Patient unable or unwilling to comply with outpatient-based treatment	
Need for more complex dressing changes than patient/caregivers can provide	
Need for careful, continuous observation	

presence or severity of foot infection or to differentiate soft tissue from bone infection. Most available studies assessed the value of blood tests, especially white blood cell (WBC) counts, ESR, CRP, and PCT, by comparing them with the results of IDSA/IWGDF criteria for infection.[9,42,54] 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 enrolled patients were recently treated with antibiotic therapy, which could affect results.

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[55-58] found little correlation with infection severity, with about half of the patients diagnosed with a DFI having a normal WBC.[59,60] In most studies, ESR values have been higher in patients with an IDFU compared with a noninfected DFU (NIDU).[55,56] ESR values can be affected by various co-morbidities (eg, anaemia and azotaemia) and may not be elevated in acute infections, due to the relatively slow response of this inflammatory biomarker, but a highly elevated ESR (≥70 mm/h) is more common in patients with bone than with just soft tissue infections.

Most studies of serum PCT levels have also found that levels were significantly higher in IDFU than NIDFU, but there was little correlation between the values and the infection severity. Furthermore, PCT has, until recently in some areas, been costlier than CRP, and it may be unavailable in many clinical laboratories. Compared with ESR, CRP levels tend to rise more quickly with infection and fall more quickly with resolution of infection. Serum values of CRP[55,56,61] have consistently been found to be significantly higher in IDFU than in NIDFU and higher in patients with NIDFU than in those with no foot ulcer, with levels increasing significantly with the severity of infection.[56,62]

Overall, CRP and PCT have shown higher diagnostic accuracy than WBC or ESR. Some studies have investigated using various combinations of these inflammatory markers, but none seemed especially useful and the highly variable cut off values make the results difficult to interpret. Serum tests for these common biomarkers are widely available, easily obtained, and most are relatively inexpensive. A few studies investigated other inflammatory markers for their role in diagnosing or following DFIs, but they were small and of low quality.[42]

PICO 2b:

In a person with diabetes and a suspected foot infection, do the IDSA/IWGDF criteria for diagnosing soft tissue infection correlate with results of skin temperature measurement or quantitative microbiology?

Recommendation 4:

As neither electronically measuring foot temperature nor using quantitative microbial analysis has been demonstrated to be useful as a method for diagnosing DFI, we suggest not using them. (Weak; low)

Rationale:

While various imaging tests are widely used for diagnosing bone infection (see PICO D3 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 foot ulcerations. A few studies have demonstrated that an increase in temperature in one area on the foot, and perhaps various photographic assessments, have a relatively weak correlation with clinical evidence of infection on examination.[63-66] Overall, employing either infrared or digital thermography does not appear to provide substantial help in diagnosing infection or predicting clinical outcome in patients with a DFU seen in the hospital setting. While infrared imaging likely has no harms, it is limited by low availability. It is possible that it may be of value when coupled to photographic assessment through telemedicine in the early diagnosis of DFI.

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.[67,68] However, there is no convincing data (from conventional culture or molecular methods) supporting this concept.[69] In the 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 cause diminished organism counts) were included, while others failed to provide information on this important confounding issue. Of note, these methods of measuring what is sometimes called "wound bioburden" are time-consuming and relatively expensive. Furthermore, neither quantitative classical culture nor molecular microbiological techniques are currently available for most clinicians in their routine practice.

PICO 3:

In a person with diabetes and suspected bone infection of the foot, which diagnostic tests best correlate with the presence of osteomyelitis, as diagnosed based on culture and/or histopathology of a bone specimen?

Recommendation 5:

In a person with diabetes and suspected osteomyelitis of the foot, we recommend using a combination of the probe-to-bone (PTB) test, the ESR (or CRP and/or PCT), and plain X-rays as the initial studies to diagnose osteomyelitis. (Strong; moderate)

Rationale:

Diagnosing osteomyelitis in the diabetic foot 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.[70] Osteomyelitis may be present underlying any DFU, 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.[71,72] Among clinical examinations, the PTB test is the most useful, but the performing clinician's technique and experience, the ulcer's location, and its aetiology may affect the test's reliability.[73,74] A systematic review of the PTB test found that for detecting DFO the sensitivity was 0.87 and specificity 0.83.[75] 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),[76] is inexpensive and essentially harmless, but interobserver agreement is only moderate.

Among blood tests, the ESR is the most useful, with a highly elevated rate (>70 mm/hr) suggesting bone infection.[57,77] Any patient with possible bone infection should initially have plain X-rays of the foot. Interpreted by an experienced reader, characteristic findings of bone infection (see Table 2) are highly suggestive of osteomyelitis, but X-rays are often negative in the first few weeks of infection and abnormal findings can be caused by Charcot osteoarthropathy and other disorders. Plain X-rays are widely available, relatively inexpensive, and associated with minimal harm. A retrospective study of 107 patients with histologically proven DFO found that after adjusting for confounders, the WBC was not useful for diagnosing DFO, but ESR (in particular), CRP, and plain radiographs were actually more useful than magnetic resonance imaging (MRI).[78]

Recommendation 6:

a) In a person with diabetes and suspected osteomyelitis of the foot, if a plain X-ray and clinical and laboratory findings are most compatible with osteomyelitis, we recommend no further imaging of the foot to establish the diagnosis. (Strong; low)
b) If the diagnosis of osteomyelitis remains in doubt, consider ordering an advanced imaging study, such as magnetic resonance imaging scan, ^{18}F-FDG-positron emission tomography (PET)/computed tomography (CT) or leukocyte scintigraphy (with or without CT). (Strong; moderate)

Rationale:

Depending on the patient setting, advanced imaging for diagnosing osteomyelitis is not needed in many patients. When needed, MRI, with a sensitivity of about 0.9 and specificity of about 0.8, has been the most widely used test for decades.[79] One retrospective study of 32 cases of pathologically proven DFO found that, compared with plain X-rays, MRI had added value in guiding surgical treatment in 65%, and a five times higher agreement with surgical findings.[80] MRI is widely available (in high income countries), with lower costs than some of the newer advanced imaging technologies, and gives an overview of the presence and anatomy of both soft tissue and bone

infections in the foot. The presence of reactive bone marrow edema from non-infectious pathologies, such as trauma, previous foot surgery or Charcot neuroarthropathy, lowers the specificity and positive predictive value.[81,82] In selected patients with possible neuro-osteoarthropathy, newer techniques such as MR angiography, dynamic contrast-enhanced MRI or neurography may better distinguish Charcot from osteomyelitis.[83-86] Newer advanced imaging tests, especially ^{18}F-fluorodeoxyglucose (FDG)-PET/CT and ^{99m}Tc-exametazime (HMPAO)-labelled leukocyte scintigraphy, can be used in patients with a contraindication to MRI and appear to have a higher specificity than MRI (especially when noninfectious bony changes are more likely) but are limited in availability, require special expertise, and are more expensive.[87,88] Compared with other nuclear medicine techniques (eg, leukocyte imaging), PET (especially with CT) offers high spatial resolution and precise anatomic localization, possibly higher sensitivity for chronic infection, easier performance, faster results, and low radiation exposure. However, currently supportive data for PET are less robust, and it is less able to differentiate infection from inflammation (including from acute Charcot foot).[89,90] The availability and cost of these advanced imaging techniques may vary in different locations, but they might be useful in situations when the diagnosis remains in doubt and there are limited options to obtain a bone biopsy. Advanced imaging (especially MRI) is also useful for surgical planning in selected cases, such as to identify purulent collections or the extent of bone involvement pre-operatively.

As with soft tissue infections (see above), it may be difficult to know when DFO has been successfully treated. There are often few clinical signs and symptoms, although resolution of 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. And some of the newer advanced imaging studies, eg, WBC-labelled SPECT/CT, FDG PET/CT, may be more sensitive in demonstrating resolution of infection. The current state of the art, however, is that DFO is at best in "remission" if diagnostic tests suggest improvement but should probably not be considered "cured" until there has been no evidence of recurrence for at least a year after the end of treatment.[91,92] An additional outcome in patients treated for DFI is recurrence of the infection at the same location. In one study of over 1000 episodes of moderate or severe DFI (including osteomyelitis), recurrent infection was noted in 25% of patients within 3 years. Risk of recurrence was higher in those with type 1 diabetes, immunosuppression, a sequestrum, who did not undergo amputation or revascularization, but was unrelated to the route or duration of antibiotic therapy.[91]

Recommendation 7:

In a person with diabetes and suspected osteomyelitis of the foot, in whom making a definitive diagnosis or determining the causative pathogen is necessary for selecting treatment, collect a sample of bone (percutaneously or surgically) to culture clinically relevant bone microorganisms and for histopathology (if possible). (Strong; low)

Rationale:

Obtaining a specimen of bone to diagnose osteomyelitis of the diabetic foot is the generally accepted criterion standard for diagnosing the infection and the only definitive way to determine the causative pathogen. Available evidence suggests that collecting a bone specimen in an aseptic manner (ie, percutaneously or per-operative, not through the wound) is safe and provides the most accurate assessment of true pathogens.[93-96] A prospective direct comparison of 46 paired per wound and transcutaneous bone biopsies in patients with suspected DFO found that results were identical in only 42%.[97] To avoid a false-negative culture, some experts suggest delaying bone biopsy in a patient receiving antibiotics until they have been off therapy for at least a few days, and ideally for at least 2 weeks.[93,94] While this seems theoretically sensible, reports from studies of various types of bone infection,[98-101] including DFO,[102] suggest that having receiving antibiotic therapy before a bone culture does not appear to reduce the percentage of positive cultures or time to culture positivity. Biopsy is generally not painful (as the majority of affected patients have sensory neuropathy), and complications are very rare.[103] While it would be theoretically useful to obtain a bone specimen in almost all cases, this is often impractical as the procedure requires some time, experience, and expense. Thus, it is most important to perform bone biopsy when it is difficult to guess the causative pathogen or its antibiotic susceptibility, eg, in patients at risk for antibiotic-resistant isolates, who have been previously treated with antibiotics or who have had a soft tissue sample that grew multiple pathogens. Biopsy may not be needed if an aseptically collected deep tissue specimen from a soft tissue infection grows only a single virulent pathogen, especially *Staphylococcus aureus*.[93,94] The diagnosis of osteomyelitis is most

TABLE 3 Features characteristic of diabetic foot osteomyelitis on plain X-rays[109-114]

- New or evolving radiographic features[a] on serial radiographs[b], including:
  - Loss of bone cortex, with bony erosion or demineralization
  - Focal loss of trabecular pattern or marrow radiolucency (demineralization)
  - 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 sequestrum[a]: devitalized 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 (eg, sequestrum, involucrum, and cloacae) are seen less frequently in diabetic foot osteomyelitis than in younger patients with osteomyelitis of larger bones.
[b]Usually spaced several weeks apart.

assured if one or more bone specimens has both a positive culture and characteristic histopathological findings.[104] Culture 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 specimen contamination is a concern. Of note, the inter-rater agreement on the diagnosis of osteomyelitis by histopathology is low (<40% in one study),[105] and concordance between histopathology and culture of foot bone specimens is also poor (41% in one study).[106] Culture of soft tissue specimens (even those collected close to the bone) often miss causative pathogens or yield likely contaminants, and thus less accurate than bone cultures. The reported concordance rates between contemporaneous cultures of soft tissue and bone are mostly ≤50% (Table 3).[93,107,108]

5 | MICROBIOLOGY

PICO 4:

In a person with diabetes and a foot infection, do specimens of wound tissue (obtained by curettage or biopsy) provide more clinically useful information on growth of pathogens or avoidance of contaminants than wound swabs?

Recommendation 8:

a) Collect an appropriate specimen for culture for almost all clinically infected ulcers to determine the causative pathogens. (Strong; low)
b) For a soft tissue DFI, obtain a sample for culture by aseptically collecting a tissue specimen (by curettage or biopsy) from the ulcer. (Strong; moderate)

Rationale:

In the great majority of cases, obtaining a specimen (after cleansing and debridement, avoiding 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, nonsevere DFI in a patient who has not recently received antibiotic therapy and has no other risk factors for unusual or antibiotic-resistant pathogens (eg, based on specific exposures or previous culture results), selecting empiric therapy without culture may be reasonable. In most clinical situations, it is easiest to collect a soft tissue specimen by superficial swab, but recent studies, including two systematic reviews[115,116] (with low-quality evidence), one small prospective study,[117] and one well-designed prospective study,[118] have generally shown that the sensitivity and specificity of tissue specimens for culture results are higher than for swabs. Collecting a tissue specimen may require slightly more training and poses a slight risk of discomfort or bleeding, but we believe the benefits clearly outweigh these minimal risks. The evidence informing what method of specimen collection to use is limited by the absence of a definitive criterion standard for defining 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 that may be contaminants rather than pathogens. A key caveat is that the accuracy of results depends on the quality of information provided between clinical and microbiology staff throughout the sample pathway, from collecting to transporting to processing to reporting. Collaboration is important: clinicians should provide key clinical details associated with the sample, and clinical microbiology services should provide adequately comprehensive reporting of the isolated organisms and their susceptibility profiles. For persons presenting in a low-income or limited resources setting without ready access to culture or follow-up care, performing a Gram-stain smear of material from a DFI could be a relatively easy and inexpensive way to visualize the class of the likely causative pathogens, thus helping direct empiric therapy.[119]

PICO 5:

In a person with diabetes and a foot infection, do the results of molecular (genotypic) microbiological tests better distinguish likely clinically relevant pathogens requiring antibiotic therapy than standard (phenotypic) cultures?

Recommendation 9:

Do not use molecular microbiology techniques (instead of conventional culture) for the first-line identification of pathogens from samples in a patient with a DFI. (Strong; low)

Rationale:

Molecular microbiology techniques have demonstrated that the flora in most DFIs is more diverse and abundant than that revealed by conventional culture methods.[120-122] Although *Corynebacterium* spp. and obligate anaerobes appear to be more prevalent using sequencing techniques, their pathogenic role as part of a polymicrobial infection is unclear.[123] Overall, there is generally good agreement between molecular sequencing and conventional culture methods regarding the most clinically relevant pathogens identified.[124] The few studies employing molecular sequencing for either soft tissue or bone infection have enrolled relatively few subjects, were at high risk of bias and have not provided information on the value of the findings for guidance on clinical management. Specifically, we do not know which of the many bacterial genera identified by molecular methods contribute to the clinical state of infection or require directed antibiotic therapy. Furthermore, molecular approaches identify both living and dead organisms and generally do not assess for the antibiotic sensitivities of identified isolates. It remains unclear whether or not determining the number of microorganisms (microbial load or operational taxonomic units) present in a

wound, or seeking gene markers for virulence factors or toxin production as a diagnostic or prognostic aid will provide any additional clinical benefits beyond current practice. Finally, compared with standard culture techniques, molecular methods may be more expensive and require more processing time, but less so using newer methods and considering the full testing pathway. Thus, for now, clinicians should continue to request conventional culture of specimens to determine the identity of causative microorganisms and their antibiotic sensitivity.

Regardless of the method of determining the causative pathogens from a specimen, collaboration, and consultation between the clinical and laboratory staff will help each to be most helpful to the other. Clinicians should provide the microbiology laboratory key clinical information (eg, type and site of infected lesion and recent antimicrobial therapy), either on order forms or by direct communication. Similarly, laboratory personnel should offer clear information (when requested) on how to obtain optimal specimens and provide preliminary and final identifications as soon as practical.

6 | TREATMENT

PICO 6: In a person with diabetes and a foot infection, is any particular antibiotic regimen (specific agent[s], route, duration) better than any other for treating soft tissue or bone infection?

6.1 | Soft tissue infection

Recommendation 10:

Treat a person with a DFI with an antibiotic agent that has been shown to be effective in a published randomized controlled trial (RCT) and is appropriate for the individual patient. Some agents to consider include penicillins, cephalosporins, carbapenems, metronidazole (in combination with other antibiotic[s]), clindamycin, linezolid, daptomycin, fluoroquinolones, or vancomycin, but not tigecycline. (Strong; high)

Recommendation 11:

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 efficacy of the agent for DFIs; risk of adverse events, including collateral damage to the commensal flora; likelihood of drug interactions; agent availability; and, financial costs. (Strong; moderate)

Recommendation 12:

Administer antibiotic therapy initially by the parenteral route to any patient with a *severe* DFI. Switch to oral therapy if the patient is clinically improving and has no contraindications to oral therapy and if there is an appropriate oral agent available. (Strong; low)

Recommendation 13:

Treat patients with a mild DFI and most with a moderate DFI, with oral antibiotic therapy, either at presentation or when clearly improving with initial intravenous therapy. (Weak; low)

Recommendation 14:

We suggest not using any currently available topical antimicrobial agent for treating a mild DFI. (Weak; moderate)

Rationale:

Antibiotic therapy, administered by an appropriate route, is required in virtually all patients with a soft tissue DFI. For mild and most moderate infections, treatment with well-absorbed oral antibiotic agents is generally effective. In patients with a more severe infection (some classification 3 and most 4), initial parenteral antibiotic therapy is to achieve immediate high serum levels, but can usually be switched to oral therapy within a week. 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 is effective in the great majority of cases.[125] Empiric therapy should be based on the clinician's best guess at the likely causative pathogen(s) and their local antibiotic susceptibilities, along with a variety of other factors (eg, history of drug allergies, recent hospitalization, patient co-morbidities [e.g., renal dialysis], likelihood of adverse events or potential drug interactions, and availability and cost of various agents). In light of the complexity and often polymicrobial nature of DFI, definitive treatment should especially be based on principles of antibiotic stewardship (preferably selecting, when appropriate, a regimen with the narrowest spectrum, shortest duration, fewest adverse effects, and safest and least expensive route). Wound culture results from a DFI are often polymicrobial; while virulent pathogens (eg, *S aureus* or beta-haemolytic streptococci) that are isolated should be treated, some less virulent isolates (eg, corynebacteria or coagulase-negative *staphylococci*) are often contaminants or colonizers that may not need targeted antibiotic treatment. Some countries or institutions restrict the use of certain antibiotics (eg, fluoroquinolones or rifampicin) for various reasons. In general, "first-line" antibiotic choices are most often well-established agents, while newer agents are often held in reserve for antibiotic-resistant pathogens. Clinicians should consider consulting an infectious diseases/microbiology expert about antibiotic therapy for difficult cases, such as those caused by unusual or highly resistant pathogens.

Treatment with topical antimicrobial therapy has many theoretical advantages, particularly using a small dose only at the site of infection, thus potentially limiting issues of cost, adverse events, and antibiotic resistance. Unfortunately, no published studies support treating either mild infections (with topical therapy alone) or moderate infections (with topical therapy adjunctive to systemic antibiotics).[126] Specifically, recent large unpublished studies of topical therapy for a mild DFI with

pexiganan (an antimicrobial peptide)[127,128] or with the gentamicin-collagen sponge[129] failed to demonstrate superiority to standard of care treatment alone. Similarly, a published trial of the gentamicin-collagen sponge for treating mild DFI[130] or as adjunctive therapy (to systemic antibiotics) for moderate or severe DFI showed no benefit.[131]

No one antibiotic class or agent has been shown to be superior to others, but tigecycline was found to be clinically inferior to ertapenem (with or without added vancomycin) for treating soft tissue (and, in a small subset, bone) infections in a well-designed clinical trial of over 1000 patients.[132] This study also showed that rates of adverse events were significantly higher in the tigecycline-treated patients. A prospective observational study of 105 patients treated with tigecycline for DFI reported clinical success in only approximately 57% of patients with a moderate or severe infection, significantly lower cure rates in those with peripheral artery disease, and adverse treatment effects in 44%.[133] Other studies have shown high failure rates with long-term treatment with tigecycline, and it is associated with a high rate of nausea.[134] Recent studies suggest that many (perhaps most) DFIs are caused by bacteria in a biofilm mode, although biofilm infection is difficult to diagnose clinically.[135,136] Pathogens in biofilm, compared with planktonic, infections are more difficult to treat, but some antibiotics (eg, rifampicin, daptomycin, and fosfomycin) appear to be more effective for biofilm infection than others.[137,138] With appropriately selected antibiotic therapy (combined with any necessary surgery and proper metabolic control and wound care), most DFIs can be treated successfully with limited harms.

Recommendation 15:

a) Administer antibiotic therapy to a patient with a skin or soft tissue DFI for a duration of 1 to 2 weeks. (Strong; high)
b) Consider continuing treatment, perhaps for up to 3 to 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. (Weak; low)
c) 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)

Rationale:

Principles of antimicrobial stewardship include limiting the duration of antibiotic therapy for treating wounds to the minimum number of days needed for good results.[139,140] More prolonged antibiotic therapy is associated with increased risks of adverse events, greater disruption of host microbiomes, higher costs, and more patient

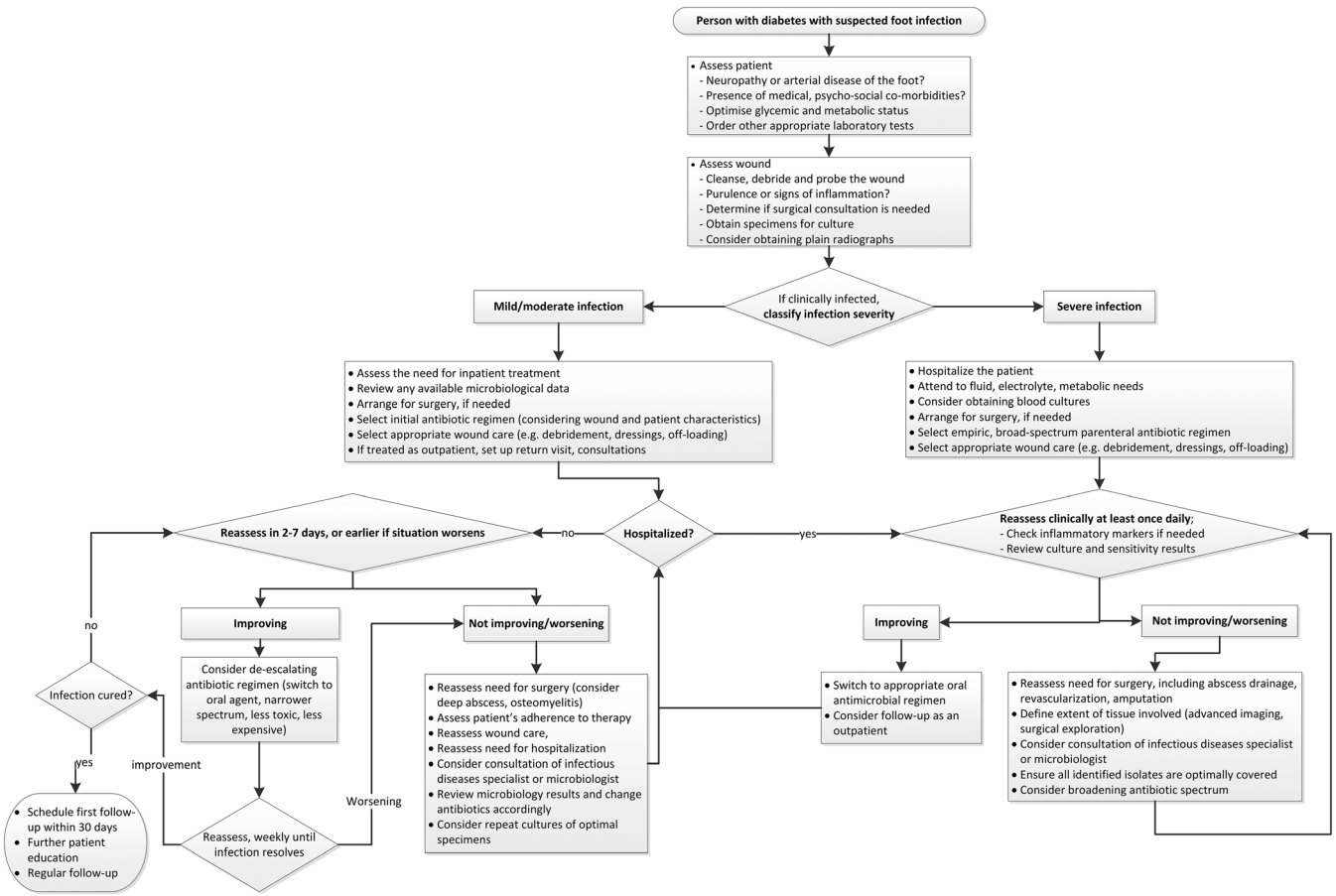

FIGURE 1 Suggested overview of a stepwise approach to managing a patient with diabetes and a suspected foot infection

inconvenience. In published studies of DFIs, duration of antibiotic therapy ranged from 5 to 28 days, but they do not provide any data upon which to recommend an optimal duration nor criteria for when stopping antibiotic therapy is appropriate.[18] In most of these studies, patients underwent any needed superficial or deep debridement of necrotic or purulent tissue and patients with severe peripheral artery disease were excluded.[51,132,141,142] Based on expert opinion, minor soft tissue infections that resolve quickly can be treated with less than 1 week of antibiotic therapy, while extending antibiotic therapy to 2 to 4 weeks may be appropriate for some patients with extensive infection or when limb ischemia limits antibiotic delivery and ulcer healing. When apparently appropriate treatment for a DFI appears to be failing, rather than extending the course of antibiotic therapy the clinician should reconsider what therapy might be more appropriate. Key questions to ask (see Figure 1) include the following: were all likely pathogens covered by the selected antibiotic agent? are there new pathogens (perhaps related to intercurrent antibiotic treatment); was the antibiotic agent being administered/taken as prescribed (whether in hospital or ambulatory setting); could intestinal absorption be impaired; was the possibility of insufficient perfusion due to peripheral artery disease not addressed; could there be an undiagnosed abscess, foreign body, osteomyelitis, or other complication that may require surgery? While the evidence for most of these suggestions is either low or limited, decades of clinical experience support our making these strong on antibiotic therapy recommendations.

Recommendation 16:

For patients who have not recently received antibiotic therapy and who reside in a temperate climate area, target empiric antibiotic therapy at just aerobic gram-positive pathogens (beta-haemolytic *streptococci* and *S aureus*) in cases of a mild DFI. (Strong; low)

Recommendation 17:

For patients residing in a tropical/subtropical climate, or who have been treated with antibiotic therapy within a few weeks, have a severely ischemic affected limb, or a moderate or severe infection, we suggest selecting an empiric antibiotic regimen that covers gram-positive pathogens, commonly isolated gram-negative pathogens, and possibly obligate anaerobes in cases of moderate to severe DFIs. Then, reconsider the antibiotic regimen based on both the clinical response and culture and sensitivity results. (Weak; low)

Recommendation 18:

Empiric treatment aimed at *Pseudomonas aeruginosa* is not usually necessary in temperate climates, but consider it if *P aeruginosa* has been isolated from cultures of the affected site within the previous few weeks, or in tropical/subtropical climates (at least for moderate or severe infection). (Weak; low)

Rationale:

Initial antibiotic therapy for most patients with a DFI will be empiric; the goal is to cover the likely pathogens without prescribing an unnecessarily broad-spectrum regimen. Definitive therapy should then be tailored to the clinical response to empiric therapy and the results of properly collected specimens. For decades, studies (almost exclusively from temperate climates in North America and Europe) consistently demonstrated that the most common pathogens in DFIs are aerobic gram-positive cocci, especially *S aureus*, and to a lesser extent streptococci and coagulase-negative staphylococci. More recent studies of DFIs from patients in tropical/subtropical climates (mainly Asia and northern Africa) have shown that aerobic gram-negative bacilli are often isolated, either alone or in combination with gram-positive cocci. These considerations, along with whether or not the patient has recently received antibiotic therapy, has had gram-negative bacilli isolated from a recent previous culture, has had frequent exposure to water (a source for *P aeruginosa*), or comes from an environment in which pathogens are often resistant to commonly used antibiotics, are key in selecting an empiric antibiotic regimen. Empiric treatment aimed at *P aeruginosa*, which usually requires either an additional or broader-spectrum agent, is generally unnecessary in temperate climates. It should, however, be considered in tropical/subtropical climates or if *P aeruginosa* has been isolated from previous cultures of the affected patient. Of course, clinicians should reassess the regimen based on the clinical response and culture and sensitivity results and consider changing to more appropriate, safer, more convenient, or less expensive agent(s).

Obligate anaerobes can play a role in a DFI, especially in ischemic limbs and in case of abscesses. [121,143] Empiric treatment of these pathogens, eg, with an imidazole (metronidazole), or beta-lactam with beta-lactamase inhibitor, should be considered for a DFI associated with ischemia or a foul-smelling discharge. Some newer cephalosporins (combined with enzyme inhibitors) and fluoroquinolones have activity against most obligate anaerobes, which might preclude the need for combining them with anti-anaerobic agents. There are, however, insufficient published data to recommend use of these agents to target anaerobes in DFIs (Table 4).

Recommendation 19:

Do not treat clinically uninfected foot ulcers with systemic or local antibiotic therapy with the goal of reducing the risk of infection or promoting ulcer healing. (Strong; low)

Rationale:

There are no convincing data to support the concept that prescribing antibiotic therapy for clinically uninfected ulcers either accelerates healing or reduces the risk of developing clinically apparent infection.[144] One study of 77 patients with an uninfected DFU followed

TABLE 4 Factors to consider in selecting an empiric antibiotic regimen for diabetic foot infections[a]

Infection severity	Additional factors	Usual pathogen(s)[c]	Potential empirical regimens[d]
Mild	No complicating features	GPC	S-S pen; first gen ceph
	ß-lactam allergy or intolerance	GPC	Clindamycin; FQ; T/S; macrolide; doxy
	Recent antibiotic exposure	GPC + GNR	ß-L-ase-1; T/S; FQ
	High risk for MRSA	MRSA	Linezolid; T/S; doxy; macrolide
Moderate or severe[e]	No complicating features	GPC ± GNR	ß-L-ase 1; second/third gen ceph
	Recent antibiotics	GPC ± GNR	ß-L-ase 2; 3rd gen ceph; group 1 carbapenem (depends on prior therapy; seek advice)
	Macerated ulcer or warm climate	GNR, including *Pseudomonas*	ß-L-ase 2; S-S pen + ceftazidime; S-S pen + cipro; group 2 carbapenem
	Ischaemic limb/necrosis/gas forming	GPC ± GNR ± Anaerobes	ß-L-ase 1 or 2; group 1 or 2 carbapenem; 2nd/3rd gen ceph + clindamycin or metronidazole
	MRSA risk factors	MRSA	Consider adding, or substituting with, glycopeptides; linezolid; daptomycin; fusidic acid T/S (±rif)[b]; doxycycline
	Risk factors for resistant GNR	ESBL	Carbapenems; FQ; aminoglycoside and colistin

Abbreviations: ß-L-ase, ß-lactam, ß-lactamase inhibitor; ß-L-ase 1, amoxicillin/clavulanate, ampicillin/sulbactam; ß-L-ase 2, ticarcillin/clavulanate, piperacillin/tazobactam; doxy, doxycycline; ESBL, extended-spectrum ß-lactamase-producing organism; FQ, fluoroquinolone with good activity against aerobic gram-positive cocci (eg, levofloxacin or moxifloxacin); gen, generation; GNR, gram-negative rod; GPC, gram-positive cocci (staphylococci and streptococci); group 1 carbapenem: ertapenem; group 2 carbapenem: imipenem, meropenem, doripenem; ceph: cephalosporin; MRSA, methicillin-resistant *Staphylococcus aureus*; Pip/tazo, piperacillin/tazobactam; S-S pen: semisynthetic penicillinase-resistant penicillin; cipro: antipseudomonal fluoroquinolone, eg, ciprofloxacin: T/S, trimethoprim/sulfamethoxazole; rif: rifamp(ic)in.

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

[b]Rifamp(ic)in: because it is associated with higher risk of adverse events and its use is restricted in some countries, it may be most appropriately used for treating osteomyelitis or metal implant related infections.

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

[d]Given at 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, obesity.

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

with repeated cultures found that no culture parameter demonstrated predictive value for any DFU outcomes.[145]

It may sometimes be difficult to know if a DFU is infected, especially in the presence of co-morbidities such as peripheral neuropathy or peripheral artery disease. For this reason, some clinicians accept "secondary" signs or symptoms, such as friable granulation tissue, ulcer undermining, foul odour, or increase in amount of exudate as evidence of infection. All open ulcers will harbour microorganisms, including ones that are potentially pathogenic, and some evidence suggests these may impair healing. And, clinically uninfected ulcers may become infected during the long time it takes for them to heal. For these (and other) reasons, many clinicians prescribe antibiotic therapy for clinically uninfected ulcers. But, there are no convincing data to support that this is beneficial. Furthermore, as about half of all DFUs are clinically uninfected at presentation, this could result in a substantial exposure of patients to potentially unnecessary and often harmful antibiotic therapy. 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) clearly outweigh any theoretical benefits.

6.2 | Surgical treatment and osteomyelitis

PICO 7a: In a person with diabetes and osteomyelitis of the foot, are there circumstances in which nonsurgical (antibiotic only) treatment is as safe and effective (in achieving remission) as surgical treatment?

Recommendation 20:

Nonsurgeons should urgently consult with a surgical specialist in cases of severe infection or of moderate infection complicated by extensive gangrene, necrotizing infection, signs suggesting deep (below the fascia) abscess or compartment syndrome, or severe lower limb ischemia. (Strong; low)

Recommendation 21:

a) In a patient with diabetes and uncomplicated forefoot osteomyelitis, for whom there is no other indication for surgical treatment, consider treating with antibiotic therapy without surgical resection of bone. (Strong; moderate)

b) In a patient with probable diabetic foot osteomyelitis with concomitant soft tissue infection, urgently evaluate for the need for surgery as well as intensive post-operative medical and surgical follow-up. (Strong; moderate)

Recommendation 22:

Select antibiotic agents for treating diabetic foot osteomyelitis from among those that have demonstrated efficacy for osteomyelitis in clinical studies. (Strong; low)

Recommendation 23:

a) Treat diabetic foot osteomyelitis with antibiotic therapy for no longer than 6 weeks. If the infection does not clinically improve within the first 2 to 4 weeks, reconsider the need for collecting a bone specimen for culture, undertaking surgical resection, or selecting an alternative antibiotic regimen. (Strong; moderate)
b) Treat diabetic foot osteomyelitis with antibiotic therapy for just a few days if there is no soft tissue infection and all the infected bone has been surgically removed. (Weak; low)

Recommendation 24:

For diabetic foot osteomyelitis cases that initially require parenteral therapy, consider switching to an oral antibiotic regimen that has high bioavailability after perhaps 5 to 7 days if the likely or proven pathogens are susceptible to an available oral agent and the patient has no clinical condition precluding oral therapy. (Weak; moderate)

Rationale:

While antibiotic therapy is necessary for DFIs, it is often not sufficient. Most patients with a DFI require some surgical treatment, ranging from minor bedside debridement or incision and drainage to major operative procedures, including resection of deep infected tissue, drainage of abscesses or infected compartments, resection of necrotic or infected bone, or revascularization. While some of these procedures can be scheduled for convenience, a few require immediate surgery. The presence or severity of deep infection is often difficult to assess and may only be identified during surgery. While there is little published evidence addressing this issue, we strongly believe the nonsurgeon should consider when and how urgently to consult with a surgeon for most DFIs.

Surgical resection of infected bone has long been the standard treatment of osteomyelitis, but over the past two decades, evidence from several retrospective case series,[146-149] one retrospective cohort study,[150] and one prospective controlled study[151] has demonstrated that in properly selected patients, antibiotic therapy alone is effective. While treatment of DFO with antibiotics without surgical resection of bone may be considered for any patient with DFO, based on published data, the strongest cases for considering nonsurgical treatment include patients with limited DFO of the forefoot, who are medically stable, for whom there is no other mechanical need for surgical treatment of the foot, and for whom there is an appropriate antibiotic regimen.[152] There are advantages and disadvantages to both predominantly surgical or medical therapy of DFO, so the clinician should involve the patient (and family) in this decision.[152]

In the absence of soft tissue infectious complications, such as deep abscesses, extensive necrosis or gangrene, tissue gas, or compartment syndrome, most cases of DFO do not require *urgent* surgery. Performing any required surgery as an elective procedure allows the treating team to decide which diagnostic studies are needed and to select appropriate empirical antibiotic therapy, as well as to prepare and educate the patient. This suggestion is largely based on expert opinion, as published studies have generally not stratified patients with DFO based on the presence or severity of any concomitant soft tissue infection. The few studies that have provided data on this issue have generally found that patients with DFO who had concomitant soft tissue infection (and perhaps those with peripheral artery disease) required more urgent and extensive surgery and had longer lengths of stay and worse outcomes.[153] One small study suggests that patients not requiring urgent surgery can be treated using a two-step approach for combined soft tissue and bone infection: prescribe antibiotic therapy (empiric if necessary, then adapted to culture results) for the soft tissue infection, followed by greater than or equal to 2-week off antibiotic therapy, then a bone biopsy (with further treatment only if it demonstrates osteomyelitis).[154] This approach requires further study.

When prescribing antibiotic therapy for DFO, the clinician must consider several issues. Penetration of antibiotic agents into bone is variable, but most classes can attain adequate levels in infected bone. We suggest administering antibiotic agents at the higher end of their recommended dosage range and usually for a total duration of treatment (see below) substantially longer than for soft tissue infection.[155] Most published studies have initially administered antibiotics parenterally, at least for a few day, but it is unclear if this is necessary. We think clinicians can prescribe initial therapy by the oral route in carefully selected patients with mild and limited soft tissue and bone infection. Many antibiotic agents have shown efficacy in treating DFO, including clindamycin, various beta-lactam beta-lactamase inhibitors (eg, ampicillin/sulbactam) and fluoroquinolones. One antibiotic agent that may (based on limited data) be particularly effective for biofilm-related staphylococcal (generally *S aureus*) infections such as DFO or hardware infections is rifampin (or rifampicin).[147,154] Data supporting this use is limited and rifampin must always be used cautiously (especially in patients taking multiple medications or at risk for tuberculosis) and combined with another agent to which the causative pathogen is susceptible (eg, a fluoroquinolone). An ongoing large, multicenter US trial (VA INTREPID) is examining the role of rifampin in treating DFO.[156] Several case series, and a recent large RCT, have shown that oral antibiotic therapy (usually after at least a few days of intravenous therapy) is as effective as, safer, and less expensive than

intravenous therapy for complex bone and joint infection (including DFO).[157]

The recommended duration of treatment for osteomyelitis has traditionally been 4 to 6 weeks, but this is based mostly on animal models and clinical experience. Some studies of DFO (and other types of osteomyelitis) have shown that therapy for longer than 6 weeks offers no additional benefit,[158] and based mostly on theoretical considerations, treatment for just 1 to 2 weeks (or less) should be sufficient for patients in whom all infected bone has been resected.[159] One retrospective cohort study of 1018 DFI episodes (including some with DFO) found that neither the duration of antibiotic therapy nor the use of parenteral therapy affected the risk of recurrence of DFI.[91] Unfortunately, there are no definitive signs or tests to inform the clinician when DFO is in remission, so long-term (usually at least a year) follow-up is recommended before declaring the infection cured. If underlying conditions that predisposed to the index episode of DFO are not adequately addressed, another infection at the same site may be a new recurrence, rather than relapse. Consideration of long-term suppressive antibiotic therapy is warranted only for individuals with retained orthopaedic hardware or extensive necrotic bone that is not amenable to complete debridement.

PICO 7b:

In a person with diabetes and osteomyelitis of the foot who is undergoing foot surgery, is obtaining biopsy of the presumed uninfected residual bone margin useful for determining the need for additional anti-infective treatment?

Recommendation 25:

a) During surgery to resect bone for diabetic foot osteomyelitis, consider obtaining a specimen of bone for culture (and, if possible, histopathology) at the stump of the resected bone to identify if there is residual bone infection. (Weak; moderate)
b) If an aseptically collected culture specimen obtained during the surgery grows pathogen(s), or if the histology demonstrates osteomyelitis, administer appropriate antibiotic therapy for up to 6 weeks. (Strong; moderate)

Rationale:

Several studies have shown that one-third to two-thirds of patients from whom the surgeon obtains a specimen of clinically uninfected bone (variously called "marginal," "distal," or "proximal" bone) after resection have culture or pathological evidence of residual infection.[160-164] This finding presumably means infected bone remains, requiring further antibiotic and/or surgical treatment. It is crucial that the bone specimen be collected as aseptically as possible, including using a new set of sterile instruments. A bone specimen obtained during an operation may be more likely than a percutaneous biopsy to be contaminated from adjoining infected soft tissue. The possibility that many of the positive bone cultures are false positives is supported by the substantially lower rate of positive histology on the same specimen in two studies.[160,163] Of course, cultures may also be falsely negative, especially in patients treated with antibiotics or when samples are not transported and processed appropriately. An additional problem is the lack of an agreed definition of osteomyelitis in the diabetic foot. As three studies have found that patients who had evidence of residual osteomyelitis after foot bone resection were significantly more likely to have poorer outcomes than those with negative bone biopsy results,[160-162] we think it would be prudent to offer most patients with a positive bone culture further anti-infective treatment.

PICO 8:

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

We define adjunctive treatments as those that are neither antibiotic nor surgical treatments, but which are often used in conjunction with these standard treatments. Many types of treatment have been proposed, but the available published evidence of their efficacy is limited and generally of very low quality.

Recommendation 26:

For a DFI, do not use hyperbaric oxygen therapy (HBOT) or topical oxygen therapy as an adjunctive treatment if the only indication is specifically for treating the infection. (Weak; low)

Rationale:

Many DFUs fail to heal, and colonising microorganisms may play a role in this process. HBOT, in addition to its purported ulcer healing benefits, is also believed to have a variety of antimicrobial effects in soft tissue and bone.[165-170] Thus, it is reasonable to consider whether or not adjunctive HBOT might help cure various types of DFIs. Several organizations (some with a bias favouring using HBOT) have suggested that HBOT should be considered for treating infections (especially anaerobic), including osteomyelitis (especially if chronic or refractory).[171] A systematic review (of case reports and cohort studies) of adjunctive HBOT treatment of various forms of chronic osteomyelitis suggested it may be beneficial, but few of the studies were on DFO and the quality of available evidence was low.[172] Notwithstanding that the role of HBOT in healing DFUs is still controversial, only one of the many studies on patients with a DFUs was specifically focused on the issue of foot infections. The results of that small size,

poor quality study,[173] using non-standardized methods and lacking clear definitions (including of infection), do not adequately support recommending HBOT to treat DFIs. HBOT is certainly associated with financial expense, potential adverse events, and inconvenience (requiring daily treatments in a medical setting). Thus, 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.

In addition to systemic HBOT, high levels of oxygen can be delivered to a wound by local or topical methods.[174] Although various methods of topical oxygen therapy have been investigated for decades, there are only a few published case reports in patients and insufficient evidence to support using this form of adjunctive treatment to address infection.[174-176]

Recommendation 27:

To specifically address infection in a diabetic foot ulcer,
a) do not use adjunctive granulocyte colony stimulating factor treatment (Weak; moderate), and
b) do not routinely use topical antiseptics, silver preparations, honey, bacteriophage therapy, or negative pressure wound therapy (NPWT) (with or without instillation). (Weak; low)

Rationale:

Because granulocyte colony-stimulating factor (G-CSF) increases the release of neutrophil endothelial progenitor cells from the bone marrow and improves neutrophil functions, which are often impaired in people with diabetes, studies have investigated their potential role in treating infection in DFUs. A Cochrane Database Systematic review updated in 2013 concluded that treatment with G-CSF does not appear to increase the likelihood of resolution of infection or healing of the foot ulcer.[177] We found no relevant published studies on this topic since this review. While G-CSF may reduce the need for surgical interventions, especially amputations, or the duration of hospitalization, it is not clear which patients might benefit, and G-CSF preparations are not generally available and are expensive.

The increasing problem of infection with antibiotic resistant organisms demands development of alternative treatments to standard antibiotic therapy. Various types of antiseptics have been used to treat DFUs, but the available evidence does not support any beneficial effect for most of these.[126] Silver has been shown to have an antibacterial effect, and topical silver-containing treatments (creams, dressings, etc) are widely used for IDFUs. While silver compounds may offer some benefits in ulcer healing,[178] there is little evidence (including from several systematic reviews) to support their effectiveness in treating or preventing ulcer infection.[179] Several small studies have, however, demonstrated anti-infective benefits for some antiseptic agents (eg, cadexomer iodine and hypochlorous solutions) in infected DFUs. There is evidence that dressings with silver, cadexomer iodine, and hypochlorous solutions reduce microbial load in the ulcers.[180,181] The available evidence is insufficient to establish whether or not silver-containing dressings or topical agents promote ulcer healing or prevent ulcer infection. To avoid promoting the development of resistance, we suggest avoid using agents topically that can also be administered systemically.

Honey has long been used in the treatment of various types of ulcers, including DFUs, for its apparent ulcer healing effects. This may at least be partly mediated by its antibacterial, antioxidant, and anti-inflammatory properties, in addition to its effects on osmolarity, acidifying pH and increasing growth factors.[182] Topical honey appears to be safe and is relatively inexpensive. Some studies have demonstrated antibacterial effects of honey on various microorganisms obtained from DFUs, either in vitro or in a wound, but there are no published studies clearly demonstrating efficacy against clinical findings of infection.[183,184] In some populations, especially in low-income countries, use of various home remedies for treating DFIs has been reported. While some may have beneficial effects (eg, chloramines[185] and *Kalanchoe pinnata*,[186]) others are clearly harmful,[187] either by their direct effects or by patients delaying seeking more appropriate treatment.

Bacteriophages have been used clinically for over 100 years, but the available data on efficacy (mostly from Eastern Europe, much of it *in vitro*) are limited. The few publications on using bacteriophages for DFUs are low-quality case series lacking a control group[188,189] that suggest it may be safe and effective for some types of infected ulcers, but commercial products are limited and unavailable in many countries. Although the incidence of infection with extensive, or even complete, antimicrobial resistance is rising in some contries, antibiotic therapy is still preferable given the sparse available evidence for bacteriophages. Antimicrobial therapy with bacteriophages might, however, be an option in the future.

NPWT involves the application of a special wound dressing attached to a vacuum suction machine that aspirates wound and tissue fluid from the treated area into a canister.[190] Some evidence demonstrates that NPWT results in more pro-angiogenic and anti-inflammatory molecular conditions in wounds.[191] NPWT with instillation (NPWTi) is a system incorporating both instillation (using one of various types of sterile fluids) and aspiration that is intended to cleanse, and possibly disinfect, wounds.[192] While many published studies have demonstrated the safety and wound healing efficacy of NPWT/NPWTi, the quality of most is relatively low, few have addressed diabetic foot complications,[193] and none have specifically addressed if there was benefit in resolving evidence of wound infection. NPWT is widely available, but in most countries rather expensive.

Several other types of adjunctive therapy look promising, but based on limited data and lack of wide availability, it is difficult to offer a recommendation on any at this time. One example is photodynamic therapy (PDT), which uses a combination of a photosensitizing drug and visible light, and has been shown in vitro to kill various bacteria, fungi, and viruses. Almost all photosensitizers show photodynamic activity against gram-positive bacteria, but activity against

gram-negative bacteria is limited to certain cationic photosensitizers. A few small published studies of low quality have reported that PDT lowered bacterial load, cured infections, and may have helped reduce lower extremity amputations.[194-197] While PDT appears to be safe and well tolerated, commercial products are not yet available in most countries, and it is unclear if using PDT without systemic antibiotic therapy will be possible for most patients.

7 | KEY CONTROVERSIES IN DFI

There is still uncertainty regarding many areas concerning the management of the infectious aspects of the diabetic foot. We have selected some that with think may be in most need of further studies.

1. How should clinicians monitor treatment of a DFI and determine when infection has resolved?
- This is an important unmet need as it serves as one means to limit unnecessarily prolonged antibiotic therapy.

2. What is the optimal duration of antimicrobial treatment for diabetic foot osteomyelitis?
- Since infection of bone is more difficult to eradicate than just sotf tissue, the recommended duration of antibiotic therapy is more prolonged, but we do not know the most appropriate duration.

3. How should clinicians adapt approaches to DFI management in low-income countries?
- The rise in incidence of DFIs in some of these countries is steep, and and with their constrained resources, finding optimal approaches, without recommending second-class care, is key to improve outcomes.

4. When, and which, imaging studies should clinicians order for a patient with a DFI?
- Advanced imaging studies can be expensive and time-consuming and may delay appropriate treatment. Thus, evaluating their cost-effectiveness to help optimize use could improve DFI (and especially DFO) management.

5. In diabetic foot osteomyelitis cases, is obtaining a specimen of residual or marginal bone after surgical resection useful for deciding which patients need further antibiotic or surgical treatment?
- Several studies suggest that a substantial minority of patients who have had surgical resection of infected bone have remaining infection in residual bone. Determining the best way to identify these cases and whether or not further treatment improves outcomes could help inform management.

6. When is it appropriate to select primarily medical versus primarily surgical treatment for diabetic foot osteomyelitis?
- While the results of a variety of types of trials inform this choice, an additional large, well-designed prospective study is needed to more definitively answer this question.

7. Is there a definition of, and practical clinical use for, the concept of wound "bacterial bioburden"?
- This term is widely used in the wound healing community (and by industry) but has no agreed upon definition. Deciding if it has value, and standardizing the definition, could help industry develop useful products and clinicians to know which to employ for selected clinical situations.

8. What is the value and proper interpretation of molecular (genotypic) microbiological testing for DFI?
- The use of molecular microbiology is inexorably expanding, but it is crucial that we have studies to provide data to help clinicians understand the value of information derived from these techniques.

9. Are there any approaches (methods or agents) to topical or local antimicrobial therapy that are effective as either sole therapy for mild infections or adjunctive treatment for moderate or severe infections?
- Although there are many types of local or topical treatment available, there is no convincing data to support if and when they should be used. These approaches, especially if they support using agents that are not administered systemically, could reduce the accelerating problem of antibiotic resistance.

10. How can clinicians identify the presence of biofilm infection and what is the best way to treat it?
- Studies suggest most chronic wound infections involve microorganisms in difficult to eradicate biofilm phenotype, but we currently have no clear information on how to diagnose or treat these infections.

8 | POSTSCRIPT

Foot infections in persons with diabetes certainly can be associated with poor outcomes, especially amputation. In a large prospective study in the United Kingdom of patients with an infected DFU, after 1 year of follow-up, the ulcer had healed in only 46%, and it recurred in 10% of those patients.[5] Among these patients with an infected DFI, 17% underwent a lower extremity amputation, 6% had a lower extremity revascularization, and 15% died. Those with a DFU present for greater than 2 months or with a higher IDSA/IWGDF score had worse outcomes. In a recent review of over 150 000 patients hospitalized for a DFI in the US, over one-third underwent a lower extremity amputation, and almost 8% had a lower-extremity revascularization procedure.[6] But studies of patients enrolled in antibiotic trials and our own experience with patients treated by interdisciplinary teams at expert centres suggest that better outcomes are possible. We think that following the principles of diagnosing and treating DFIs outlined in this guideline can help clinicians

to provide better care for these at-risk patients. We also encourage our colleagues, especially those working in diabetic foot clinics or hospital wards, to consider developing some forms of surveillance (eg, registries, pathways, and interdisciplinary group meetings) to monitor and attempt to improve their outcomes in patients with DFIs.

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CONFLICT OF INTEREST

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REFERENCES

1. International Diabetes Federation. Diabetes Atlas, 8th edition, http://www.diabetesatlas.org/. 2019.
2. Raspovic KM, Wukich DK. Self-reported quality of life and diabetic foot infections. *J Foot Ankle Surg*. 2014;53:716-719.
3. Peters EJ, Childs MR, Wunderlich RP, Harkless LB, Armstrong DG, Lavery LA. Functional status of persons with diabetes-related lower-extremity amputations. *Diabetes Care*. 2001;24:1799-1804.
4. Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. *Clin Infect Dis*. 2007;44:562-565.
5. Ndosi M, Wright-Hughes A, Brown S, et al. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. *Diabet Med*. 2018;35:78-88.
6. Tan TW, Shih CD, Concha-Moore KC, et al. Disparities in outcomes of patients admitted with diabetic foot infections. *PLoS One*. 2019;14:e0211481.
7. Zha ML, Cai JY, Chen HL. A bibliometric analysis of global research production pertaining to diabetic foot ulcers in the past ten years. *J Foot Ankle Surg*. 2019;58:253-259.
8. Paisley AN, Kalavalapalli S, Subudhi CP, Chadwick PR, Chadwick PJ, Young B. Real time presence of a microbiologist in a multidisciplinary diabetes foot clinic. *Diabetes Res Clin Pract*. 2012;96:e1-e3.
9. Lipsky BA, Aragon-Sanchez J, Diggle M, et al. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. *Diabetes Metab Res Rev*. 2016;32(Suppl 1):45-74.
10. Peters EJ, Lipsky BA, Aragon-Sanchez J, et al. Interventions in the management of infection in the foot in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2016;32(Suppl 1):145-153.
11. Lipsky BA, Berendt AR, Deery HG, et al. Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2004;39:885-910.
12. Lipsky BA, Berendt AR, Embil J, de Lalla F. Diagnosing and treating diabetic foot infections. *Diabetes Metab Res Rev*. 2004;20:S56-S64.
13. Peters EJ, Lipsky BA. Diagnosis and management of infection in the diabetic foot. *Med Clin North Am*. 2013;97:911-946.
14. Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infections in individuals with diabetes. *Diabetes Care*. 2006;29:1288-1293.
15. Hao D, Hu C, Zhang T, Feng G, Chai J, Li T. Contribution of infection and peripheral artery disease to severity of diabetic foot ulcers in Chinese patients. *Int J Clin Pract*. 2014;68:1161-1164.
16. Peters EJ, Lavery LA, Armstrong DG. Diabetic lower extremity infection: influence of physical, psychological, and social factors. *J Diabetes Complications*. 2005; Mar-Apr;19:107-112.
17. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE study. *Diabetologia*. 2008;51:747-755.
18. Chu Y, Wang C, Zhang J, et al. Can we stop antibiotic therapy when signs and symptoms have resolved in diabetic foot infection patients? *Int J Low Extrem Wounds*. 2015;14:277-283.
19. Acosta JB, del Barco DG, Vera DC, et al. The pro-inflammatory environment in recalcitrant diabetic foot wounds. *Int Wound J*. 2008;5:530-539.
20. Berlanga-Acosta J. Diabetic lower extremity wounds: the rationale for growth factors-based infiltration treatment. *Int Wound J*. 2011;8:612-620.
21. Lavery LA, Peters EJ, Armstrong DG, Wendel CS, Murdoch DP, Lipsky BA. Risk factors for developing osteomyelitis in patients with diabetic foot wounds. *Diabetes Res Clin Pract*. 2009;83:347-352.
22. McMahon MM, Bistrian BR. Host defenses and susceptibility to infection in patients with diabetes mellitus. *Infect Dis Clin North Am*. 1995;9:1-9.
23. Perner A, Nielsen SE, Rask-Madsen J. High glucose impairs superoxide production from isolated blood neutrophils. *Intensive Care Med*. 2003;29:642-645.
24. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. *Diabet Med*. 1997;14:29-34.
25. Callahan D, Keeley J, Alipour H, et al. Predictors of severity in diabetic foot infections. *Ann Vasc Surg*. 2016;33:103-108.
26. Uckay I, Jornayvaz FR, Lebowitz D, Gastaldi G, Gariani K, Lipsky BA. An overview on diabetic foot infections, including issues related to associated pain, hyperglycemia and limb ischemia. *Curr Pharm des*. 2018;24:1243-1254.
27. Aragon-Sanchez J, Lazaro-Martinez JL, Pulido-Duque J, Maynar M. From the diabetic foot ulcer and beyond: how do foot infections spread in patients with diabetes? *Diabet Foot Ankle*. 2012;3.
28. Bridges RM Jr, Deitch EA. Diabetic foot infections. Pathophysiology and treatment. *Surg Clin North Am*. 1994;74:537-555.
29. Maharaj D, Bahadursingh S, Shah D, Chang BB, Darling RC. Sepsis and the scalpel: anatomic compartments and the diabetic foot. *Vasc Endovascular Surg*. 2005;39:421-423.

30. Richard JL, Lavigne JP, Sotto A. Diabetes and foot infection: more than double trouble. *Diabetes Metab Res Rev*. 2012;28(Suppl 1): 46-53.
31. Sotto A, Richard JL, Jourdan N, Combescure C, Bouziges N, Lavigne JP. Miniaturized oligonucleotide arrays: a new tool for discriminating colonization from infection due to *Staphylococcus aureus* in diabetic foot ulcers. *Diabetes Care*. 2007;30:2051-2056.
32. Lavery LA, Peters EJ, Williams JR, Murdoch DP, Hudson A, Lavery DC. Reevaluating the way we classify the diabetic foot: restructuring the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. *Diabetes Care*. 2008;31: 154-156.
33. Wukich DK, Hobizal KB, Brooks MM. Severity of diabetic foot infection and rate of limb salvage. *Foot Ankle Int*. 2013;34:351-358.
34. Tobalem M, Uckay I. Images in clinical medicine. Evolution of a diabetic foot infection. *N Engl J Med*. 2013;369:2252.
35. National Institute for Health and Clinical Excellence. Diabetic foot–inpatient management of people with diabetic foot ulcers and infection. http://guidanceniceorguk/CG119 2011.
36. Alonso-Coello P, Oxman AD, Moberg J, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: clinical practice guidelines. *BMJ*. 2016;353:i2089.
37. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336:924-926.
38. Jeffcoate WJ, Bus SA, Game FL, et al. Reporting standards of studies and papers on the prevention and management of foot ulcers in diabetes: required details and markers of good quality. *Lancet Diabetes Endocrinol*. 2016;4:781-788.
39. Senneville É, Lipsky BA, Abbas ZG, et al. Diagnosis of infection in the foot in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(S1):e3281.
40. Peters EJG, Lipsky BA, Senneville É, et al. Interventions in the management of infection in the foot in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2020;36(S1):e3282.
41. Bus SA, van Netten JJ, Hinchliffe RJ, Apelqvist J, Lipsky BA, Schaper NC, IWGDF Editorial Board. Standards for the development and methodology of the 2019 International Working Group on the Diabetic Foot guidelines. *Diabetes Metab Res Rev*. 2020;36(S1):e3267.
42. Ozer Balin S, Sagmak Tartar A, Ugur K, et al. Pentraxin-3: a new parameter in predicting the severity of diabetic foot infection? *Int Wound J*. 2019;16:659-664.
43. Pickwell K, Siersma V, Kars M, et al. Predictors of lower-extremity amputation in patients with an infected diabetic foot ulcer. *Diabetes Care*. 2015;38:852-857.
44. Seth A, Attri AK, Kataria H, Kochhar S, Seth SA, Gautam N. Clinical profile and outcome in patients of diabetic foot infection. *Int J Appl Basic Med Res*. 2019;9:14-19.
45. Royal College of Physicians. National Early Warning Score (NEWS). Standardising the assessment of acute-illness severity in the NHS. Report of a working party. London, RCP 2012.
46. Smith GB, Prytherch DR, Meredith P, Schmidt PE, Featherstone PI. The ability of the National Early Warning Score (NEWS) to discriminate patients at risk of early cardiac arrest, unanticipated intensive care unit admission, and death. *Resuscitation*. 2013;84:465-470.
47. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for Sepsis and septic shock (Sepsis-3). *JAMA*. 2016;315:801-810.
48. Ince P, Abbas ZG, Lutale JK, et al. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. *Diabetes Care*. 2008;31:964-967.
49. Zhan LX, Branco BC, Armstrong DG, Mills JL Sr. The Society for Vascular Surgery lower extremity threatened limb classification system based on wound, ischemia, and foot infection (WIfI) correlates with risk of major amputation and time to wound healing. *J Vasc Surg*. 2015;61:939-944.
50. Monteiro-Soares M, Russel D, Boyko EJ, et al. *IWGDF Guideline on Classification of Diabetic Foot Ulcers*. Publication pending; 2019.
51. Lipsky BA, Pecoraro RE, Larson SA, Hanley ME, Ahroni JH. Outpatient management of uncomplicated lower-extremity infections in diabetic patients. *Arch Intern Med*. 1990;150:790-797.
52. Commons RJ, Raby E, Athan E, et al. Managing diabetic foot infections: a survey of Australasian infectious diseases clinicians. *J Foot Ankle Res*. 2018;11:13.
53. Barwell ND, Devers MC, Kennon B, et al. Diabetic foot infection: antibiotic therapy and good practice recommendations. *Int J Clin Pract*. 2017;71:e13006.
54. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012;54:e132-e173.
55. Uzun G, Solmazgul E, Curuksulu H, et al. Procalcitonin as a diagnostic aid in diabetic foot infections. *Tohoku J Exp Med*. 2007;213: 305-312.
56. Park JH, Suh DH, Kim HJ, Lee YI, Kwak IH, Choi GW. Role of procalcitonin in infected diabetic foot ulcer. *Diabetes Res Clin Pract*. 2017;128:51-57.
57. Al-Shammaree SAW, Abu ABA, Salman IN. Procalcitonin levels and other biochemical parameters in patients with or without diabetic foot complications. *J Res Med Sci*. 2017;22:95.
58. Korkmaz P, Kocak H, Onbasi K, et al. The role of serum procalcitonin, interleukin-6, and fibrinogen levels in differential diagnosis of diabetic foot ulcer infection. *J Diabetes Res*. 2018;2018: 7104352.
59. Armstrong DG, Perales TA, Murff RT, Edelson GW, Welchon JG. Value of white blood cell count with differential in the acute diabetic foot infection. *J Am Podiatr Med Assoc*. 1996;86:224-227.
60. Eneroth M, Apelqvist J, Stenstrom A. Clinical characteristics and outcome in 223 diabetic patients with deep foot infections. *Foot Ankle Int*. 1997;18:716-722.
61. Jeandrot A, Richard JL, Combescure C, et al. Serum procalcitonin and C-reactive protein concentrations to distinguish mildly infected from non-infected diabetic foot ulcers: a pilot study. *Diabetologia*. 2008;51:347-352.
62. Umapathy D, Dornadula S, Rajagopalan A, et al. Potential of circulatory procalcitonin as a biomarker reflecting inflammation among South Indian diabetic foot ulcers. *J Vasc Surg*. 2018;67:1283-1291e2.
63. van Netten JJ, Prijs M, van Baal JG, Liu C, van der Heijden F, Bus SA. Diagnostic values for skin temperature assessment to detect diabetes-related foot complications. *Diabetes Technol Ther*. 2014;16: 714-721.
64. Hazenberg CE, van Netten JJ, van Baal SG, Bus SA. Assessment of signs of foot infection in diabetes patients using photographic foot imaging and infrared thermography. *Diabetes Technol Ther*. 2014;16: 370-377.
65. Liu C, van Netten JJ, van Baal JG, Bus SA, van der Heijden F. Automatic detection of diabetic foot complications with infrared thermography by asymmetric analysis. *J Biomed Opt*. 2015;20:26003.
66. Armstrong DG, Lipsky BA, Polis AB, Abramson MA. Does dermal thermometry predict clinical outcome in diabetic foot infection? Analysis of data from the SIDESTEP* trial. *Int Wound J*. 2006;3: 302-307.
67. Gardner SE, Frantz RA. Wound bioburden and infection-related complications in diabetic foot ulcers. *Biol Res Nurs*. 2008;10:44-53.
68. Gardner SE, Hillis SL, Frantz RA. Clinical signs of infection in diabetic foot ulcers with high microbial load. *Biol Res Nurs*. 2009;11:119-128.
69. Kallstrom G. Are quantitative bacterial wound cultures useful? *J Clin Microbiol*. 2014;52:2753-2756.

70. Meyr AJ, Seo K, Khurana JS, Choksi R, Chakraborty B. Level of agreement with a multi-test approach to the diagnosis of diabetic foot osteomyelitis. *J Foot Ankle Surg*. 2018;57:1137-1139.
71. Lipsky BA. Osteomyelitis of the foot in diabetic patients. *Clin Infect Dis*. 1997;25:1318-1326.
72. Lázaro-Martínez JL, Tardáguila-García A, García-Klepzig JL. Diagnostic and therapeutic update on diabetic foot osteomyelitis. *Endocrinología, Diabetes y Nutrición (English Ed)*. 2017;64:100-108.
73. Senneville E. Editorial commentary: probe-to-bone test for detecting diabetic foot osteomyelitis: rapid, safe, and accurate-but for which patients? *Clin Infect Dis*. 2016;63:949-950.
74. Alvaro-Afonso FJ, Lazaro-Martinez JL, Aragon-Sanchez J, Garcia-Morales E, Garcia-Alvarez Y, Molines-Barroso RJ. Inter-observer reproducibility of diagnosis of diabetic foot osteomyelitis based on a combination of probe-to-bone test and simple radiography. *Diabetes Res Clin Pract*. 2014;105:e3-e5.
75. Lam K, van Asten SA, Nguyen T, La Fontaine J, Lavery LA. Diagnostic accuracy of probe to bone to detect osteomyelitis in the diabetic foot: a systematic review. *Clin Infect Dis*. 2016;63:944-948.
76. Grayson ML, Gibbons GW, Balogh K, Levin E, Karchmer AW. Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. 1995:721–3.
77. van Asten SA, Jupiter DC, Mithani M, La Fontaine J, Davis KE, Lavery LA. Erythrocyte sedimentation rate and C-reactive protein to monitor treatment outcomes in diabetic foot osteomyelitis. *Int Wound J*. 2017;14:142-148.
78. Ramanujam CL, Han D, Zgonis T. Medical imaging and laboratory analysis of diagnostic accuracy in 107 consecutive hospitalized patients with diabetic foot osteomyelitis and partial foot amputations. *Foot Ankle Spec*. 2018;11:433-443.
79. Dinh MT, Abad CL, Safdar N. Diagnostic accuracy of the physical examination and imaging tests for osteomyelitis underlying diabetic foot ulcers: meta-analysis. *Clin Infect Dis*. 2008;47:519-527.
80. Cohen M, Cerniglia B, Gorbachova T, Horrow J. Added value of MRI to X-ray in guiding the extent of surgical resection in diabetic forefoot osteomyelitis: a review of pathologically proven, surgically treated cases. *Skeletal Radiol*. 2019;48:405-411.
81. Baker JC, Demertzis JL, Rhodes NG, Wessell DE, Rubin DA. Diabetic musculoskeletal complications and their imaging mimics. *Radiographics*. 2012;32:1959-1974.
82. Chatha DS, Cunningham PM, Schweitzer ME. MR imaging of the diabetic foot: diagnostic challenges. *Radiol Clin North Am*. 2005;43:747-759. ix.
83. Cildag MB, Ertugrul BM, Koseoglu OF, Cildag S, Armstrong DG. Angiographic assessment of atherosclerotic load at the lower extremity in patients with diabetic foot and charcot neuro-arthropathy. *J Chin Med Assoc*. 2018;81:565-570.
84. Cildag MB, Ertugrul MB, Koseoglu OF, Armstrong DG. A factor increasing venous contamination on bolus chase three-dimensional magnetic resonance imaging: Charcot neuroarthropathy. *J Clin Imaging Sci*. 2018;8:13.
85. Ertugrul BM, Lipsky BA, Savk O. Osteomyelitis or Charcot neuro-osteoarthropathy? Differentiating these disorders in diabetic patients with a foot problem. *Diabet Foot Ankle*. 2013;4:10.3402/dfa.v4i0.21855.
86. Martin Noguerol T, Luna Alcala A, Beltran LS, Gomez Cabrera M, Broncano Cabrero J, Vilanova JC. Advanced MR imaging techniques for differentiation of neuropathic arthropathy and osteomyelitis in the diabetic foot. *Radiographics*. 2017;37:1161-1180.
87. Lauri C, Tamminga M, Glaudemans AWJM, et al. Detection of osteomyelitis in the diabetic foot by imaging techniques: a systematic review and meta-analysis comparing MRI, white blood cell scintigraphy, and FDG-PET. *Diabetes Care*. 2017;40:1111-1120.
88. Rastogi A, Bhattacharya A, Prakash M, et al. Utility of PET/CT with fluorine-18-fluorodeoxyglucose-labeled autologous leukocytes for diagnosing diabetic foot osteomyelitis in patients with Charcot's neuroarthropathy. *Nucl Med Commun*. 2016;37:1253-1259.
89. Arnon-Sheleg E, Keidar Z. Diabetic foot infection: the role of PET/-CT imaging. *Curr Pharm des*. 2018;24:1277-1286.
90. Yousaf S, Dawe EJC, Saleh A, Gill IR, Wee A. The acute Charcot foot in diabetics: diagnosis and management. *EFORT Open Rev*. 2018;3:568-573.
91. Gariani K, Lebowitz D, von Dach E, Kressmann B, Lipsky BA, Uckay I. Remission in diabetic foot infections: duration of antibiotic therapy and other possible associated factors. *Diabetes Obes Metab*. 2019;21:244-251.
92. Vouillarmet J, Morelec I, Thivolet C. Assessing diabetic foot osteomyelitis remission with white blood cell SPECT/CT imaging. *Diabet Med*. 2014;31:1093-1099.
93. Senneville E, Melliez H, Beltrand E, et al. Culture of percutaneous bone biopsy specimens for diagnosis of diabetic foot osteomyelitis: concordance with ulcer swab cultures. *Clin Infect Dis*. 2006;42:57-62.
94. Senneville E, Morant H, Descamps D, et al. Needle puncture and transcutaneous bone biopsy cultures are inconsistent in patients with diabetes and suspected osteomyelitis of the foot. *Clin Infect Dis*. 2009;48:888-893.
95. Aslangul E, M'Bemba J, Caillat-Vigneron N, et al. Diagnosing diabetic foot osteomyelitis in patients without signs of soft tissue infection by coupling hybrid 67Ga SPECT/CT with bedside percutaneous bone puncture. *Diabetes Care*. 2013;36:2203-2210.
96. Letertre-Gibert P, Desbiez F, Vidal M, et al. Blood cultures after bone biopsy in diabetic foot osteomyelitis. *Diagn Microbiol Infect Dis*. 2017;89:78-79.
97. Couturier A, Chabaud A, Desbiez F, et al. Comparison of microbiological results obtained from per-wound bone biopsies versus transcutaneous bone biopsies in diabetic foot osteomyelitis: a prospective cohort study. *Eur J Clin Microbiol Infect Dis*. 2019;38:1287-1291.
98. Beroukhim G, Shah R, Bucknor MD. Factors predicting positive culture in CT-guided bone biopsy performed for suspected osteomyelitis. *AJR Am J Roentgenol*. 2019;212:620-624.
99. Wu JS, Gorbachova T, Morrison WB, Haims AH. Imaging-guided bone biopsy for osteomyelitis: are there factors associated with positive or negative cultures? *AJR Am J Roentgenol*. 2007;188:1529-1534.
100. Anagnostopoulos A, Bossard DA, Ledergerber B, et al. Perioperative antibiotic prophylaxis has no effect on time to positivity and proportion of positive samples: a cohort study of 64 *Cutibacterium* acnes bone and joint infections. *J Clin Microbiol*. 2018;56(2):e01576–17.
101. Agarwal V, Wo S, Lagemann GM, Tsay J, Delfyett WT. Image-guided percutaneous disc sampling: impact of antecedent antibiotics on yield. *Clin Radiol*. 2016;71:228-234.
102. Aragón-Sánchez FJ, Cabrera-Galván JJ, Quintana-Marrero Y, et al. Outcomes of surgical treatment of diabetic foot osteomyelitis: a series of 185 patients with histopathological confirmation of bone involvement. *Diabetologia*. 2008;51:1962-1970.
103. Elamurugan TP, Jagdish S, Kate V, Chandra Parija S. Role of bone biopsy specimen culture in the management of diabetic foot osteomyelitis. *Int J Surg*. 2011;9:214-216.
104. Berendt AR, Peters EJ, Bakker K, et al. Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment. *Diabetes Metab Res Rev*. 2008;24:S145-S161.
105. Meyr AJ, Singh S, Zhang X, et al. Statistical reliability of bone biopsy for the diagnosis of diabetic foot osteomyelitis. *J Foot Ankle Surg*. 2011;50:663-667.
106. Elmarsafi T, Kumar A, Cooper PS, et al. Concordance between bone pathology and bone culture for the diagnosis of osteomyelitis in the presence of Charcot neuro-osteoarthropathy. *J Foot Ankle Surg*. 2018;57:919-923.

107. Ertugrul MB, Baktiroglu S, Salman S, et al. Pathogens isolated from deep soft tissue and bone in patients with diabetic foot infections. *J Am Podiatr Med Assoc*. 2008;98:290-295.
108. Zuluaga AF, Galvis W, Jaimes F, Vesga O. Lack of microbiological concordance between bone and non-bone specimens in chronic osteomyelitis: an observational study. *BMC Infect Dis*. 2002;2:2-8.
109. Newman LG, Waller J, Palestro CJ, et al. Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. *JAMA*. 1991;266:1246-1251.
110. Yuh WT, Corson JD, Baraniewski HM, et al. Osteomyelitis of the foot in diabetic patients: evaluation with plain film, 99mTc-MDP bone scintigraphy, and MR imaging. *AJR Am J Roentgenol*. 1989;152:795-800.
111. Weinstein D, Wang A, Chambers R, Stewart CA, Motz HA. Evaluation of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections. *Foot Ankle*. 1993;14:18-22.
112. Mettler MA. *Essentials of Radiology*. Elsevier Saunders: Philadephia, PA; 2005.
113. Vartanians VM, Karchmer AW, Giurini JM, Rosenthal DI. Is there a role for imaging in the management of patients with diabetic foot? *Skeletal Radiol*. 2009;38:633-636.
114. Alvaro-Afonso FJ, Lazaro-Martinez JL, Garcia-Morales E, Garcia-Alvarez Y, Sanz-Corbalan I, Molines-Barroso RJ. Cortical disruption is the most reliable and accurate plain radiographic sign in the diagnosis of diabetic foot osteomyelitis. *Diabet Med*. 2019;36:258-259.
115. O'Meara S, Nelson EA, Golder S, et al. Systematic review of methods to diagnose infection in foot ulcers in diabetes. *Diabet Med*. 2006; 23:341-347.
116. Nelson EA, O'Meara S, Craig D, et al. A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers. *Health Technol Assess* 2006;10:iii-iv, ix-x, 1–221.
117. Huang Y, Cao Y, Zou M, et al. A comparison of tissue versus swab culturing of infected diabetic foot wounds. *Int J Endocrinol*. 2016; 2016:8198714.
118. Nelson A, Wright-Hughes A, Backhouse MR, et al. CODIFI (concordance in diabetic foot ulcer infection): a cross-sectional study of wound swab versus tissue sampling in infected diabetic foot ulcers in England. *BMJ Open*. 2018;8:e019437.
119. Abbas ZG, Lutale JK, Ilondo MM, Archibald LK. The utility of Gram stains and culture in the management of limb ulcers in persons with diabetes. *Int Wound J*. 2012;9:677-682.
120. Noor S, Raghav A, Parwez I, Ozair M, Ahmad J. Molecular and culture based assessment of bacterial pathogens in subjects with diabetic foot ulcer. *Diabetes Metab Syndr*. 2018;12:417-421.
121. Percival SL, Malone M, Mayer D, Salisbury AM, Schultz G. Role of anaerobes in polymicrobial communities and biofilms complicating diabetic foot ulcers. *Int Wound J*. 2018;15:776-782.
122. Malone M, Johani K, Jensen SO, et al. Next generation DNA sequencing of tissues from infected diabetic foot ulcers. *EBioMedicine*. 2017;21:142-149.
123. Johani K, Fritz BG, Bjarnsholt T, et al. Understanding the microbiome of diabetic foot osteomyelitis: insights from molecular and microscopic approaches. *Clin Microbiol Infect*. 2019;25:332–339.
124. Malone M, Gosbell IB, Dickson HG, Vickery K, Espedido BA, Jensen SO. Can molecular DNA-based techniques unravel the truth about diabetic foot infections? *Diabetes Metab Res Rev*. 2017;33: e2834.
125. Selva Olid A, Sola I, Barajas-Nava LA, Gianneo OD, Bonfill Cosp X, Lipsky BA. Systemic antibiotics for treating diabetic foot infections. *Cochrane Database Syst Rev*. 2015;CD009061.
126. Dumville JC, Lipsky BA, Hoey C, Cruciani M, Fiscon M, Xia J. Topical antimicrobial agents for treating foot ulcers in people with diabetes. *Cochrane Database Syst Rev*. 2017;6:CD011038.
127. Pexiganan versus placebo control for the treatment of mild infections of diabetic foot ulcers (OneStep-2). Clinicaltrialsgov 2017; NCT01594762.
128. Pexiganan versus placebo control for the treatment of mild infections of diabetic foot ulcers (OneStep-1). Clinicaltrialsgov 2017; NCT01590758.
129. Safety and efficacy of an antibiotic sponge in diabetic patients with a mild infection of a foot ulcer. Clinicaltrialsgov 2012;NCT00 593567.
130. Uckay I, Kressmann B, Di Tommaso S, et al. A randomized controlled trial of the safety and efficacy of a topical gentamicin-collagen sponge in diabetic patients with a mild foot ulcer infection. *SAGE Open Med*. 2018;6:205031211877395.
131. Uckay I, Kressmann B, Malacarne S, et al. A randomized, controlled study to investigate the efficacy and safety of a topical gentamicin-collagen sponge in combination with systemic antibiotic therapy in diabetic patients with a moderate or severe foot ulcer infection. *BMC Infect Dis*. 2018;18:361.
132. Lauf L, Ozsvar Z, Mitha I, et al. Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot infections with and without osteomyelitis. *Diagn Microbiol Infect Dis*. 2014;78:469-480.
133. Arda B, Uysal S, Tasbakan M, et al. Use of tigecycline for diabetic foot infections. *Wounds*. 2017;29:297-305.
134. Ingram PR, Rawlins MD, Murray RJ, Roberts JA, Manning L. Tigecycline use in the outpatient parenteral antibiotic therapy setting. *Eur J Clin Microbiol Infect Dis*. 2016;35:1673-1677.
135. Hurlow JJ, Humphreys GJ, Bowling FL, McBain AJ. Diabetic foot infection: a critical complication. *Int Wound J*. 2018;15:814-821.
136. Johani K, Malone M, Jensen S, et al. Microscopy visualisation confirms multi-species biofilms are ubiquitous in diabetic foot ulcers. *Int Wound J*. 2017;14:1160-1169.
137. Vatan A, Saltoglu N, Yemisen M, et al. Association between biofilm and multi/extensive drug resistance in diabetic foot infection. *Int J Clin Pract*. 2018;72:e13060.
138. Lebeaux D, Ghigo JM, Beloin C. Biofilm-related infections: bridging the gap between clinical management and fundamental aspects of recalcitrance toward antibiotics. *Microbiol Mol Biol Rev*. 2014;78: 510-543.
139. Lipsky BA, Dryden M, Gottrup F, Nathwani D, Seaton RA, Stryja J. Antimicrobial stewardship in wound care: a position paper from the British Society for Antimicrobial Chemotherapy and European wound management association. *J Antimicrob Chemother*. 2016;71: 3026-3035.
140. Uckay I, Berli M, Sendi P, Lipsky BA. Principles and practice of antibiotic stewardship in the management of diabetic foot infections. *Curr Opin Infect Dis*. 2019;32:95-101.
141. Siami G, Christou N, Eiseman I, Tack KJ. Clinafloxacin versus piperacillin-tazobactam in treatment of patients with severe skin and soft tissue infections. *Antimicrob Agents Chemother*. 2001;45: 525-531.
142. Vick-Fragoso R, Hernández-Oliva G, Cruz-Alcázar J, et al. Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections. *Infection*. 2009;37:407-417.
143. Charles PG, Uckay I, Kressmann B, Emonet S, Lipsky BA. The role of anaerobes in diabetic foot infections. *Anaerobe*. 2015;34:8-13.
144. Abbas M, Uckay I, Lipsky BA. In diabetic foot infections antibiotics are to treat infection, not to heal wounds. *Expert Opin Pharmacother*. 2015;16:821-832.
145. Gardner SE, Haleem A, Jao YL, et al. Cultures of diabetic foot ulcers without clinical signs of infection do not predict outcomes. *Diabetes Care*. 2014;37:2693-2701.
146. Ulcay A, Karakas A, Mutluoglu M, Uzun G, Turhan V, Ay H. Antibiotherapy with and without bone debridement in diabetic foot osteomyelitis: a retrospective cohort study. *Pak J Med Sci*. 2014;30:28-31.
147. Senneville E, Lombart A, Beltrand E, et al. Outcome of diabetic foot osteomyelitis treated nonsurgically: a retrospective cohort study. *Diabetes Care*. 2008;31:637-642.

148. Game FL, Jeffcoate WJ. Primarily non-surgical management of osteomyelitis of the foot in diabetes. *Diabetologia*. 2008;51:962-967.
149. Acharya S, Soliman M, Egun A, Rajbhandari SM. Conservative management of diabetic foot osteomyelitis. *Diabetes Res Clin Pract*. 2013;101:e18-e20.
150. Lesens O, Desbiez F, Theis C, et al. *Staphylococcus aureus*-related diabetic osteomyelitis: medical or surgical management? A French and Spanish retrospective cohort. *Int J Low Extrem Wounds*. 2015; 14:284-290.
151. Lázaro-Martínez JL, Aragón-Sánchez J, García-Morales E. Antibiotics versus conservative surgery for treating diabetic foot osteomyelitis: a randomized comparative trial. *Diabetes Care*. 2014;37: 789-795.
152. Lipsky BA. Treating diabetic foot osteomyelitis primarily with surgery or antibiotics: have we answered the question? *Diabetes Care*. 2014;37:593-595.
153. Aragon-Sanchez J, Lipsky BA. Modern management of diabetic foot osteomyelitis. The when, how and why of conservative approaches. *Expert Rev Anti Infect Ther*. 2018;16:35-50.
154. Berthol N, Robineau O, Boucher A, et al. Two-step sequential approach for concomitant skin and soft tissue infection and osteomyelitis complicating the diabetic foot. *Diabetes Care*. 2017;40:e170-e171.
155. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. *Clin Infect Dis*. 2012;54:393-407.
156. VA Office of Research and Development. CSP #2001 - Investigation of rifampin to reduce pedal amputations for osteomyelitis in diabetics (VA Intrepid). Clinicaltrialsgov 2017;NCT03012529.
157. Li HK, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. *N Engl J Med*. 2019;380:425-436.
158. Tone A, Nguyen S, Devemy F, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. *Diabetes Care*. 2015;38:302-307.
159. Senneville E, Nguyen S. Current pharmacotherapy options for osteomyelitis: convergences, divergences and lessons to be drawn. *Expert Opin Pharmacother*. 2013;14:723-734.
160. Kowalski TJ, Matsuda M, Sorenson MD, Gundrum JD, Agger WA. The effect of residual osteomyelitis at the resection margin in patients with surgically treated diabetic foot infection. *J Foot Ankle Surg*. 2011;50:171-175.
161. Atway S, Nerone VS, Springer KD, Woodruff DM. Rate of residual osteomyelitis after partial foot amputation in diabetic patients: a standardized method for evaluating bone margins with intraoperative culture. *J Foot Ankle Surg*. 2012;51:749-752.
162. Hachmoller A. Outcome of minor amputations at the diabetic foot in relation to bone histopathology: a clinical audit. *Zentralbl Chir*. 2007; 132:491-496.
163. Mijuskovic B, Kuehl R, Widmer AF, et al. Culture of bone biopsy specimens overestimates rate of residual osteomyelitis after toe or forefoot amputation. *J Bone Joint Surg Am*. 2018;100:1448-1454.
164. Schmidt BM, McHugh JB, Patel RM, Wrobel JS. Prospective analysis of surgical bone margins after partial foot amputation in diabetic patients admitted with moderate to severe foot infections. *Foot Ankle Spec*. 2018:12:131–137.
165. Mathieu D. Role of hyperbaric oxygen therapy in the management of lower extremity wounds. *Int J Low Extrem Wounds*. 2006;5:233-235.
166. Mader JT, Brown GL, Guckian JC, Wells CH, Reinarz JA. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. *J Infect Dis*. 1980;142:915-922.
167. Park MK, Myers RA, Marzella L. Oxygen tensions and infections: modulation of microbial growth, activity of antimicrobial agents, and immunologic responses. *Clin Infect Dis*. 1992;14:720-740.
168. Memar MY, Ghotaslou R, Samiei M, Adibkia K. Antimicrobial use of reactive oxygen therapy: current insights. *Infect Drug Resist*. 2018; 11:567-576.
169. Cimsit M, Uzun G, Yildiz S. Hyperbaric oxygen therapy as an anti-infective agent. *Expert Rev Anti Infect Ther*. 2009;7:1015-1026.
170. Memar MY, Yekani M, Alizadeh N, Baghi HB. Hyperbaric oxygen therapy: antimicrobial mechanisms and clinical application for infections. *Biomed Pharmacother*. 2019;109:440-447.
171. Mathieu D, Marroni A, Kot J. Tenth European consensus conference on hyperbaric medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb Med*. 2017;47:24-32.
172. Savvidou OD, Kaspiris A, Bolia IK, et al. Effectiveness of hyperbaric oxygen therapy for the Management of Chronic Osteomyelitis: a systematic review of the literature. *Orthopedics*. 2018;41:193-199.
173. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. *J Postgrad Med*. 1992;38:112-114. 1.
174. Dissemond J, Kroger K, Storck M, Risse A, Engels P. Topical oxygen wound therapies for chronic wounds: a review. *J Wound Care*. 2015; 24:53-54. 6–60, 2–3.
175. Game FL, Apelqvist J, Attinger C, et al. Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. *Diabetes Metab Res Rev*. 2016;32(Suppl 1):154-168.
176. Everett E, Mathioudakis N. Update on management of diabetic foot ulcers. *Ann N Y Acad Sci*. 2018;1411:153-165.
177. Cruciani M, Lipsky BA, Mengoli C, de Lalla F. Granulocyte-colony stimulating factors as adjunctive therapy for diabetic foot infections. *Cochrane Database Syst Rev*. 2013;CD006810.
178. Dissemond J, Bottrich JG, Braunwarth H, Hilt J, Wilken P, Munter KC. Evidence for silver in wound care—meta-analysis of clinical studies from 2000-2015. *J Dtsch Dermatol Ges*. 2017;15:524-535.
179. Tsang KK, Kwong EW, Woo KY, To TS, Chung JW, Wong TK. The anti-inflammatory and antibacterial action of nanocrystalline silver and Manuka honey on the molecular alternation of diabetic foot ulcer: a comprehensive literature review. *Evid Based Complement Alternat Med*. 2015;2015:218283.
180. Malone M, Johani K, Jensen SO, et al. Effect of cadexomer iodine on the microbial load and diversity of chronic non-healing diabetic foot ulcers complicated by biofilm in vivo. *J Antimicrob Chemother*. 2017; 72:2093-2101.
181. Schwartz JA, Lantis JC, Gendics C, Fuller AM, Payne W, Ochs D. A prospective, non comparative, multicenter study to investigate the effect of cadexomer iodine on bioburden load and other wound characteristics in diabetic foot ulcers. *Int Wound J*. 2013;10: 193-199.
182. Kateel R, Adhikari P, Augustine AJ, Ullal S. Topical honey for the treatment of diabetic foot ulcer: a systematic review. *Complement Ther Clin Pract*. 2016;24:130-133.
183. Kateel R, Bhat G, Baliga S, Augustine AJ, Ullal S, Adhikari P. Antibacterial action of tropical honey on various bacteria obtained from diabetic foot ulcer. *Complement Ther Clin Pract*. 2018;30:29-32.
184. Jull AB, Cullum N, Dumville JC, Westby MJ, Deshpande S, Walker N. Honey as a topical treatment for wounds. *Cochrane Database Syst Rev*. 2015;CD005083.
185. Bergqvist K, Almhojd U, Herrmann I, Eliasson B. The role of chloramines in treatment of diabetic foot ulcers: an exploratory multicentre randomised controlled trial. *Clin Diabetes Endocrinol*. 2016; 2:6.
186. Cawich SO, Harnarayan P, Budhooram S, Bobb NJ, Islam S, Naraynsingh V. Wonder of life (*Kalanchoe pinnata*) leaves to treat diabetic foot infections in Trinidad & Tobago: a case control study. *Trop Doct*. 2014;44:209-213.
187. Cawich SO, Harnarayan P, Islam S, et al. Topical "soft candle" applications for infected diabetic foot wounds: a cause for concern? *Int J Biomed Sci*. 2014;10:111-117.
188. Morozova VV, Kozlova YN, Ganichev DA, Tikunova NV. Bacteriophage treatment of infected diabetic foot ulcers. *Methods Mol Biol*. 2018;1693:151-158.

189. Fish R, Kutter E, Wheat G, Blasdel B, Kutateladze M, Kuhl S. Compassionate use of bacteriophage therapy for foot ulcer treatment as an effective step for moving toward clinical trials. *Methods Mol Biol*. 2018;1693:159-170.
190. Liu Z, Dumville JC, Hinchliffe RJ, et al. Negative pressure wound therapy for treating foot wounds in people with diabetes mellitus. *Cochrane Database Syst Rev*. 2018;10:CD010318.
191. Borys S, Hohendorff J, Frankfurter C, Kiec-Wilk B, Malecki MT. Negative pressure wound therapy use in diabetic foot syndrome-from mechanisms of action to clinical practice. *Eur J Clin Invest*. 2019;49:e13067.
192. Kim PJ, Attinger CE, Crist BD, et al. Negative pressure wound therapy with instillation: review of evidence and recommendations. *Wounds*. 2015;27:S2-S19.
193. Dale AP, Saeed K. Novel negative pressure wound therapy with instillation and the management of diabetic foot infections. *Curr Opin Infect Dis*. 2015;28:151-157.
194. Morley S, Griffiths J, Philips G, et al. Phase IIa randomized, placebo-controlled study of antimicrobial photodynamic therapy in bacterially colonized, chronic leg ulcers and diabetic foot ulcers: a new approach to antimicrobial therapy. *Br J Dermatol*. 2013;168:617-624.
195. Tardivo JP, Adami F, Correa JA, Pinhal MA, Baptista MS. A clinical trial testing the efficacy of PDT in preventing amputation in diabetic patients. *Photodiagnosis Photodyn Ther*. 2014;11:342-350.
196. Tardivo JP, Serrano R, Zimmermann LM, et al. Is surgical debridement necessary in the diabetic foot treated with photodynamic therapy? *Diabet Foot Ankle*. 2017;8:1373552.
197. Mannucci E, Genovese S, Monami M, et al. Photodynamic topical antimicrobial therapy for infected foot ulcers in patients with diabetes: a randomized, double-blind, placebo-controlled study—the D.A.N.T.E (Diabetic ulcer Antimicrobial New Topical treatment Evaluation) study. *Acta Diabetol*. 2014;51:435-440.

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