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SUPPLEMENT ARTICLE

IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes

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Recommendations

Classification/diagnosis

1. Diabetic foot infection must be diagnosed clinically, based on the presence of local or systemic signs or symptoms of inflammation (strong; low).
2. 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).

Osteomyelitis

3. For an infected open wound, perform a probe-to-bone test; in a patient at low risk for osteomyelitis, a negative test largely rules out the diagnosis, while in a high-risk patient, a positive test is largely diagnostic (strong; high).
4. Markedly elevated serum inflammatory markers, especially erythrocyte sedimentation rate, are suggestive of osteomyelitis in suspected cases (weak; moderate).
5. A definite diagnosis of bone infection usually requires positive results on microbiological (and, optimally, histological) examinations of an aseptically obtained bone sample, but this is usually required only when the diagnosis is in doubt or determining the causative pathogen's antibiotic susceptibility is crucial (strong; moderate).
6. A probable diagnosis of bone infection is reasonable if there are positive results on a combination of diagnostic tests, such as probe-to-bone, serum inflammatory markers, plain X-ray, magnetic resonance imaging (MRI) or radionuclide scanning (strong; weak).
7. Avoid using results of soft tissue or sinus tract specimens for selecting antibiotic therapy for osteomyelitis as they do not accurately reflect bone culture results (strong; moderate).
8. Obtain plain X-rays of the foot in all cases of non-superficial diabetic foot infection (strong; low).
9. Use MRI when an advanced imaging test is needed for diagnosing diabetic foot osteomyelitis (strong; moderate).
10. When MRI is not available or contraindicated, consider a white blood cell-labelled radionuclide scan, or possibly single-photon emission computed tomography (CT) and CT (SPECT/CT) or fluorine-18-fluorodeoxyglucose positron emission tomography/CT scans (weak; moderate).

Assessing severity

11. At initial evaluation of any infected foot, obtain vital signs and appropriate blood tests, debride the wound and probe and assess the depth and extent of the infection to establish its severity (strong; moderate).

12. At initial evaluation, assess arterial perfusion and decide whether and when further vascular assessment or revascularization is needed (strong; low).

Microbiological considerations

13. Obtain cultures, preferably of a tissue specimen rather than a swab, of infected wounds to determine the causative microorganisms and their antibiotic sensitivity (strong; high).
14. Do not obtain repeat cultures unless the patient is not clinically responding to treatment, or occasionally for infection control surveillance of resistant pathogens (strong; low).
15. Send collected specimens to the microbiology laboratory promptly, in sterile transport containers, accompanied by clinical information on the type of specimen and location of the wound (strong; low).

Surgical treatment

16. Consult a surgical specialist in selected cases of moderate, and all cases of severe, diabetic foot infection (weak; low).
17. Perform urgent surgical interventions in cases of deep abscesses, compartment syndrome and virtually all necrotizing soft tissue infections (strong; low).
18. Consider surgical intervention in cases of osteomyelitis accompanied by spreading soft tissue infection, destroyed soft tissue envelope, progressive bone destruction on X-ray or bone protruding through the ulcer (strong; low).

Antimicrobial therapy

19. While virtually all clinically infected diabetic foot wounds require antimicrobial therapy, do not treat clinically uninfected wounds with antimicrobial therapy (Strong; Low)
20. Select specific antibiotic agents for treatment based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy of the agent for diabetic foot infection and costs (strong; moderate).
21. A course of antibiotic therapy of 1–2 weeks is usually adequate for most mild and moderate infections (strong; high).
22. Administer parenteral therapy initially for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding (strong; low).
23. Do not select a specific type of dressing for a diabetic foot infection with the aim of preventing an infection or improving its outcome (strong; high).
24. For diabetic foot osteomyelitis, we recommend 6 weeks of antibiotic therapy for patients who do not undergo resection of infected bone and no more than a week of antibiotic treatment if all infected bone is resected (strong; moderate).
25. We suggest not using any adjunctive treatments for diabetic foot infection (weak; low).
26. When treating a diabetic foot infection, assess for use of traditional remedies and previous antibiotic use and consider local bacterial pathogens and their susceptibility profile (strong; low).

Introduction

In recent decades, as the prevalence of diabetes has increased, so too have foot complications, including infections. The development of a foot infection is associated with substantial morbidity, including discomfort, reduced physical and mental quality of life [1], need for healthcare provider visits, wound care, antimicrobial therapy and often surgical procedures. Furthermore, foot infection remains the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputation [2–5]. Managing infection requires careful attention to properly diagnosing the condition, obtaining appropriate specimens for culture, thoughtfully selecting empirical and then definitive antimicrobial therapy, quickly determining when surgical interventions are needed and providing all other necessary types of wound care. For these reasons, interdisciplinary teams should, whenever possible, include an infectious diseases or clinical microbiology specialist [6]. A systematic and, to the extent possible, evidence-based approach to diabetic foot infections (DFIs) should result in better outcomes.

This report from the expert panel on infectious diseases of the International Working Group on the Diabetic Foot (IWGDF) is an update of the one published in 2012 [7]. It incorporates some information from the concurrently published 'Systematic Review of Interventions in the Management of Infection in the Diabetic Foot' [8] as well as non-systematic reviews of the literature covering each of the sections in this guidance. Our intention is to present a brief overview to assist clinicians worldwide in diagnosing and treating foot infections in persons with diabetes. This document follows the newly adopted format of all IWGDF guidance documents, including providing recommendations that are

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rated based on the Grading of Recommendations Assessment, Development and Evaluation system.[1]

Pathophysiology

In persons with diabetes, foot infection is an increasingly common problem that is related to the duration of the disease and therefore the likelihood of diabetic complications. 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. DFI is defined clinically as manifestations of this process in soft tissue or bone anywhere below the malleoli in a person with diabetes. These infections usually begin with a break in the protective cutaneous envelope, typically in a site of trauma or ulceration [9]. Peripheral neuropathy (mostly sensory but also motor and autonomic) is the main factor leading to skin breaks; these open wounds then become colonized (usually with skin flora) and, in many cases, ultimately infected. Foot ischaemia, related to peripheral arterial disease, is also common in patients with a DFI. While rarely the primary cause of foot wounds, the presence of limb ischaemia increases the risk of a wound becoming infected [10,11] and adversely affects the outcome of infection [5,12]. Foot wounds in diabetic patients often become chronic, related to hyperglycemia-induced advanced glycation end products, persistent inflammation and apoptosis [13,14]. Factors that predispose to foot infection include having a wound that is deep, long-standing or recurrent, or of traumatic aetiology; ill-defined diabetes-related immunological perturbations related to neutrophil dysfunction; and chronic renal failure [10,15–18].

While most DFIs are relatively superficial at presentation, microorganisms can spread contiguously to subcutaneous tissues, including fascia, tendons, muscle, joints and bone. The anatomy of the foot, which is divided into several rigid but intercommunicating compartments, fosters proximal spread of infection [19]. The inflammatory response induced by infection may cause compartmental pressure to exceed capillary pressure, leading to ischaemic tissue necrosis [20,21]. 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. Strains of *Staphylococcus aureus* isolated from clinically non-infected ulcers have been shown to have a lower virulence potential than from ulcers that are infected [22]. Similarly, a clonal complex 398 methicillin-susceptible *S. aureus* with a tropism for bone has emerged as the main staphylococcal pathogen in one outbreak of diabetic foot osteomyelitis (DFO) [23].

Systemic symptoms (e.g. feverishness and chills), marked leukocytosis 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 [5]. If not diagnosed and properly treated, DFIs tend to progress, sometimes rapidly [24]. Thus, an experienced consultant (or team) should see a patient with a severe DFI within 24 h [25].

Diagnosis and classification

1. Diabetic foot infection must be diagnosed clinically, based on the presence of local and systemic signs and symptoms of inflammation (strong; moderate).
2. Assess the severity of any DFI using the Infectious Diseases Society of America (IDSA)/IWGDF classification scheme (strong; moderate).

Rationale

The clinician seeing a patient with a diabetic foot wound should first assess for the presence of a DFI and, if present, classify the infection's severity. Over the past three decades, experts have proposed many classification schemes for diabetic foot wounds. Most of these take into account the size and depth of the ulcer and the presence or absence of gangrene, neuropathy or arterial insufficiency. Several diabetic foot ulcer classifications only include the presence or absence of 'infection' (which is undefined). Only two, nearly identical, schemes proposed by the IDSA and the IWGDF (the 'infection' part of the PEDIS classification) describe how to define both the presence and severity of infection (Table 1) [26–29]. Several other guidelines, including ones produced by the Spanish, French and UK (NICE), have adopted the IDSA/IWGDF infection classification [25,30–32].

The full PEDIS system (which includes classification of other wound descriptors, such as arterial disease, neuropathy and wound size) of the IWGDF was originally developed for research purposes, but it can serve as a

[1]Recommendations in this guidance were formulated based on the Grading of Recommendations Assessment, Development and Evaluation system for grading evidence when writing a clinical guideline [112]. For much of the older data found in the systematic review underlying this guidance, we could not calculate or assess for inconsistency, indirectness or imprecision, which are needed to fully assess the quality of evidence. Therefore, we decided to assess the quality of evidence on the risk of bias of included studies, effect sizes and expert opinion and rate the quality of evidence as 'high', 'moderate' or 'low'. We assessed the strength of each recommendation as 'strong' or 'weak', based on the quality of evidence, balance between benefits and harms, patient values and preferences, and costs (resource utilization). The rationale behind each recommendation is described in this guidance.

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clinical classification as well [28,33]. Classification of DFIs using the full PEDIS system [34,35] or the infection part of the IWGDF/IDSA DFI scheme [5] has been shown in several prospective studies to predict the need for hospitalization or lower extremity amputation. Two recently published retrospective cohort studies from one centre addressed the issue of whether or not the presence of systemic inflammatory response syndrome findings, which separate moderate from severe infections, actually predicts outcomes. They assessed the differences in outcome between hospitalized patients without and with systemic inflammatory response syndrome (i.e. PEDIS grade 3 *versus* grade 4) with a DFI [36,37]. In one study, patients with grade 4 infections experienced a 7.1-fold higher risk of major amputation and had a 4-day longer mean hospital stay compared with patients with grade 3 infections [36]. In the other publication, patients with grade 4 compared with grade 3 DFI had a significantly longer length of hospital stay (8 *versus* 5 days) and a non-significantly lower limb salvage rate (80% *versus* 94%) [37]. Another recently published retrospective cohort study reviewed outcomes in 57 DFI patients according to the level of adherence of their clinicians to the IDSA practice guidelines [38]. They found that rates of adherence to various recommendations ranged from very high to very low, but in none of the patient treatment courses did clinicians adhere to all. In this small and suboptimally designed study, adherence to the recommendations was not related to clinical outcome, but patients with severe infections were more likely to have adverse outcomes. Surprisingly, appropriate empiric and targeted antibiotic therapy was associated with treatment failure.

Soft tissue infection

Because all skin wounds harbour microorganisms, their mere presence (even if they are virulent species) cannot be taken as evidence of infection. Some maintain that the presence of high numbers of bacteria (usually defined as $\geq 10^5$ colony-forming units per gram per tissue) should be a basis for diagnosing infection [39], but no convincing data support this concept for wounds, including in the diabetic foot [40]. Furthermore, quantitative microbiology is rarely available outside of research laboratories. Thus, DFI must be diagnosed clinically (Table 1), with wound cultures serving to determine the causative organisms and their antibiotic sensitivities.

Clinicians should evaluate a diabetic patient presenting with a foot wound at three levels: the patient as a whole (e.g. cognitive, metabolic and fluid status), the affected foot or limb (e.g. the presence of neuropathy and vascular insufficiency) and the infected wound [29]. Clinical diagnosis rests on the presence of at least two local findings of inflammation, that is, redness (erythema or rubor), warmth (calor), pain or tenderness (dolor), induration (swelling or tumour) or purulent secretions [28,41]. Other (sometimes called secondary) features suggestive of infection include the presence of necrosis, friable or discoloured granulation tissue, non-purulent secretions, foetid odour or the failure of a properly treated wound to heal [42]. These findings may be helpful when local and systemic

Table 1. The classification systems for defining the presence and severity of an infection of the foot in a person with diabetes developed by the Infectious Diseases Society of America (IDSA) and the infection part of the PEDIS classification of the International Working Group on the Diabetic Foot (IWGDF) [28,29]

Clinical classification of infection, with definitions	IWGDF/IDSA classification
Uninfected: no systemic or local symptoms or signs of infection	1 (uninfected)
Infected - At least two of the following items are present: • Local swelling or induration • Erythema >0.5 cm* around the wound • Local tenderness or pain • Local warmth • Purulent discharge - Other causes of an inflammatory response of the skin should be excluded (e.g. trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis and venous stasis)	
- Infection involving only the skin or subcutaneous tissue (without involvement of deeper tissues and without systemic manifestations as described next) - Any erythema present extends <2 cm* around the wound - No systemic signs or symptoms of infection (see the following discussions)	2 (mild infection)
- Infection involving structures deeper than skin and subcutaneous tissues (e.g. bone, joint, tendon or muscle) or erythema extending ≥2 cm* from the wound margin - No systemic signs or symptoms of infection (see the following details)	3 (moderate infection)
- Any foot infection with the systemic inflammatory response syndrome, as manifested by ≥2 of the following: • Temperature >38 °C or <36 °C • Heart rate >90 beats/min • Respiratory rate >20 breaths/min or PaCO2 <4.3 kPa (32 mmHg) • White blood cell count >12 000/mm^3 or <4000/mm^3, or >10% immature (band) forms	4 (severe infection)

*In any direction, from the rim of the wound. The presence of clinically significant foot ischaemia makes both diagnosis and treatment of infection considerably more difficult.

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inflammatory signs are diminished because of peripheral neuropathy or ischaemia [43–45]. Because infection can worsen quickly, clinicians must pursue the diagnosis methodically [43] and aggressively [46]. All wounds must be carefully inspected, palpated and probed, both at initial presentation and on follow-up. Various imaging and laboratory studies may be useful in some cases to define the extent of soft tissue infection and any bone involvement.

Osteomyelitis

3. For an infected open wound, perform a probe-to-bone test; in a patient at low risk for osteomyelitis, a negative test largely rules out the diagnosis, while in a high-risk patient, a positive test is largely diagnostic (strong; high).
4. Markedly elevated serum inflammatory markers, especially erythrocyte sedimentation rate, are suggestive of osteomyelitis in suspected cases (weak; moderate).
5. A definite diagnosis of bone infection usually requires positive results on both histological (and optimally microbiological) examinations of an aseptically obtained bone sample, but this is usually required only when the diagnosis is in doubt or determining the causative pathogen's antibiotic susceptibility is crucial (strong; moderate).
6. A probable diagnosing of bone infection is reasonable if there are positive results on a combination of diagnostic tests, such as probe-to-bone, serum inflammatory markers, plain X-ray, MRI or radionuclide scanning (strong; weak).
7. Avoid using results of soft tissue or sinus tract specimens for selecting antibiotic therapy for osteomyelitis as they do not accurately reflect bone culture results (strong; moderate).
8. Obtain plain X-rays of the foot in all cases of non-superficial DFI (strong; low).
9. Use MRI when an advanced imaging test is needed for diagnosing DFO (strong; moderate).
10. When MRI is not available or contraindicated, consider a white blood cell-labelled radionuclide scan, or possibly single-photon emission computed tomography (CT) and computed tomography (SPECT/CT) or fluorine-18-fluorodeoxyglucose positron emission tomography (PET) scans (weak; moderate).

Rationale

Diabetic foot osteomyelitis can present the clinician with formidable diagnostic and therapeutic challenges [47]. It is found in ~50–60% of patients hospitalized for a DFI and ~10–20% of apparently less severe infections presenting in the ambulatory setting. Bone infection typically involves the forefoot (and less often the hindfoot) and develops by contiguous spread from overlying soft tissue, penetration through the cortical bone and into the medullary cavity. Bone destruction related to Charcot neuro-osteoarthropathy (CN) may be difficult to distinguish from DFO, but it is less common, generally occurs in patients with profound peripheral neuropathy (but usually adequate arterial perfusion), usually affects the midfoot and most often occurs in the absence of a skin break [48–50]. Many cases of DFO are monomicrobial, but most are polymicrobial, with *S. aureus* the most commonly isolated pathogen (found in ~50% of cases), while coagulase-negative staphylococci (~25%), aerobic streptococci (~30%) and Enterobacteriaceae (~40%) are other frequent isolates [48].

Accurately diagnosing bone infection can be difficult but is essential to ensure appropriate treatment. A definite diagnosis of osteomyelitis requires both the presence of histological findings consistent with bone infection (acute or chronic inflammatory cells, necrosis) and the isolation of bacteria from an aseptically obtained bone sample [51]. Because bone sampling and processing are not routinely available in many settings, clinicians must often use surrogate diagnostic markers, including clinical, laboratory and imaging findings.

The clinical presentation of osteomyelitis in the diabetic foot can vary with the site involved, the extent of infected and dead bone, the presence of any associated abscess or soft tissue involvement, the causative organism(s) and the adequacy of limb perfusion. The main problems in diagnosing osteomyelitis are that there is a delay in the ability to detect bony changes in early infection on plain radiographs, while later when bony changes occur, it may be difficult to distinguish on imaging studies those caused by infection from those related to CN. As discussed next, analyses from recent expert publications [51,52] and systematic reviews [51,53–55] provide guidance on the best available diagnostic studies for DFO.

Clinical evaluation

Clinicians should suspect osteomyelitis when an ulcer lies over a bony prominence, particularly when it fails to heal despite adequate off-loading, or when a toe is erythematous and indurated (the so-called 'sausage toe'). The likelihood ratio (LR) of a clinician's suspicion of osteomyelitis is surprisingly good, with a positive LR 5.5 and negative LR 0.54 [53,54]. Based on one study, the presence of exposed bone has a positive LR for osteomyelitis of 9.2; large ulcers (area >2 cm^2) are much more likely to have underlying bone infection (positive LR 7.2) than smaller ones (negative LR 0.70) [53,54,56,57]. Osteomyelitis can, however, occur in the absence of overlying local signs of inflammation [56].

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Probe-to-bone test

In the past two decades, there have been at least seven published studies of the probe-to-bone test [50]. When performed correctly and interpreted appropriately, this is a useful clinical tool for diagnosing DFO. If a blunt sterile metal probe gently inserted through a wound strikes bone (detected by its hard, gritty feel), this substantially increases the likelihood (positive LR 7.2) that the patient has osteomyelitis if the prevalence of bone infection is high (i.e. greater than ~60%) in the population under scrutiny [58,59]. Conversely, a negative probe-to-bone test in a patient at low risk (i.e. less than or equal to ~20%) essentially rules out osteomyelitis (negative LR 0.48) [60–62]. The inter-observer variability of the test is relatively high for inexperienced clinicians compared with experienced ones, but low between experienced clinicians [63]. One study found a stronger correlation among clinicians' results for ulcers located in the hallux and in the central metatarsals compared with the lesser toes [64]. Combining the results of the probe-to-bone test with those of plain radiography improves overall diagnostic accuracy of osteomyelitis [58,63].

Blood tests

The erythrocyte sedimentation rate has proven to be useful in diagnosing DFO; a highly elevated (usually defined as >70 mm/h) level increases the likelihood of osteomyelitis underlying a diabetic foot wound (positive LR of 11), while lower levels reduce the likelihood (negative LR of 0.34) [53,65–68]. Based on fewer data, a highly elevated C-reactive protein, procalcitonin or blood leukocyte count may be suggestive of osteomyelitis. These latter tests tend to revert to normal levels within a week of treatment [69], while the erythrocyte sedimentation rate drops more slowly and can therefore be useful for monitoring response to therapy. There is insufficient evidence to support the routine use of any other biomarkers to document bone infection in the diabetic foot. A preliminary report suggested that interleukin-6, but not interleukin-8, may be useful in the diagnosis and follow-up of DFI [70–72]. Combining laboratory testing with clinical findings may improve the diagnostic accuracy for osteomyelitis [73].

Imaging studies

Plain radiography. Plain X-rays are often sufficient for imaging the foot in patients with suspicion of DFO. Characteristic features of osteomyelitis on plain X-rays of the foot are summarized in Table 2. Advantages of this imaging test are that it is widely available (even in most centres with limited resources), has a relatively low cost, can be adequately read by most experienced clinicians and is relatively easy to compare sequential radiographs over time. In addition to bony changes, plain radiographs can demonstrate the presence of gas in the soft tissues or radiopaque foreign bodies. The results of two systematic reviews suggest that radiographic findings are only marginally predictive of osteomyelitis if positive and even less predictive of the absence of osteomyelitis if negative [53,54]. While the reported sensitivity of radiography varies considerably in reported studies [56,74–81], the estimated positive LR is 2.3, and negative LR is 0.63 [55]. The timing of the imaging greatly influences its usefulness, as longer-standing cases are far more likely to show bony abnormalities on plain radiographs than those present for less than 2–3 weeks. We know of no study that has evaluated sequential plain radiographs of the foot over time, but changes seen over an interval of at least 2 weeks are more likely to predict the presence of osteomyelitis than a single study. Of course, effective antibiotic therapy may prevent these bony changes from occurring. Advanced imaging techniques are expensive, often limited in availability and difficult to interpret by a non-expert. Thus, they are usually needed only when there is persistent doubt about the diagnosis of DFO or in the context of preparing a surgical intervention.

Table 2. Typical features of diabetic foot osteomyelitis on plain X-rays* [56,74,75,269]

- Periosteal reaction or elevation
- Loss of bone cortex with bony erosion
- Focal loss of cortical trabecular pattern or marrow radiolucency
- Bone sclerosis, with or without erosion
- Presence of sequestrum: devitalized bone with radiodense appearance that has become separated from normal bone
- Presence of involucrum: a layer of new bone growth outside previously existing bone resulting from stripping off of the periosteum and new bone growing from the periosteum
- Presence of cloacae: opening in the involucrum or cortex through which sequestrae or granulation tissue may discharge
- Presence of evidence of a sinus tract from the bone to the soft tissue

*Some features (e.g. sequestrum, involucrum and cloacae) are seen less frequently in diabetic foot osteomyelitis than in younger patients with osteomyelitis of larger bones.

Magnetic resonance imaging. Magnetic resonance imaging (MRI) is a valuable tool for diagnosing osteomyelitis, as well as defining the presence and anatomy of deep soft tissue infections [29,54,82]. The key features suggestive of osteomyelitis on MRI are low focal signal intensity on T1-weighted images, high focal signal on T2-weighted images and high bone marrow signal in short tau inversion recovery (STIR) sequences. Meta-analyses have found that the sensitivity of MRI for DFO is about 90% and the specificity about 85%, diagnostic odds ratio (OR) of 24 [54,82] and LRs estimated at positive of 3.8 and negative of 0.14. More recently performed studies reported lower diagnostic ORs compared with older ones, perhaps because they employed better study designs. The

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subgroups of patients with other diagnoses (e.g. CN) were too small to analyse any differences among the studies. A recent study found that MRI was effective in distinguishing DFO from bone marrow oedema in neuropathic ulcers but was less accurate for the diagnosis of DFO in ischemic ulcers, presumably because of their insufficient interstitial fluid [83].

Nuclear medicine scans. Among the several types of nuclear imaging procedures, a bone scan, usually performed with ^{99m}Tc-methylene diphosphonate in time-sequence phases, has been used for the longest time and is considered suggestive of osteomyelitis when it discloses increased blood-pool activity and radionuclide intensity localized to the bone [54]. Three-phase bone scans are reasonably sensitive (~80–90%) but not specific (~30–45%) [84]; their positive predictive value is only 65% and the pooled diagnostic OR only 2.1 with positive LR of 1.4 and negative LR of 0.40 [55]. One meta-analysis found the performance characteristics of a triple-phase bone scan markedly inferior to MRI [82]. Thus, a positive bone scan is certainly not specific for osteomyelitis (or CN), especially in the forefoot, but a negative one largely rules it out [84].

Radio-labelled white blood cells (usually using either ^{99m}Technetium or ^{111}Indium) are generally not taken up by healthy bone, making a positive leukocyte scan more specific than a bone scan for diagnosing osteomyelitis (and excluding CN) [84]. The positive predictive values for leukocyte scans for osteomyelitis are about 70–90% and the negative predictive values about 80% [84], the sensitivity is about 75–80% and specificity about 70–85%, and the positive LR 2.3 and negative LR 0.38 [55,85]. Labelling with ^{99m}Tc rather than with ^{111}In appears to provide superior physical characteristics, leading to better spatial resolution [85]. Most nuclear medicine authorities suggest that among radionuclide procedures, labelled leukocyte imaging is the best choice for evaluating DFO [54,56], but MRI generally outperforms leukocyte scanning [80,82,86,87]. Some advocate combining a labelled leukocytes scan with a bone scan (dual-tracer technique), but this does not substantially improve diagnostic accuracy [88].

More recently, studies have shown that using combined ^{99m}Tc white blood cell-labelled single-photon emission computed tomography and computed tomography (^{99m}Tc WBC-labelled SPECT/CT) imaging provides good spatial resolution with the three-dimensional CT-scan images and WBC uptake intensity yielding more information about the location and extent of infection. Although previous studies have demonstrated the value of SPECT/CT for diagnosing inflammatory bone lesions, most focused on larger osseous structures than the foot [85,89]. In a small series of patients with suspected DFO, ^{99m}Tc WBC SPECT/CT demonstrated a sensitivity of 87.5%, specificity of 71.4%, positive predictive value of 83.3% and negative predictive value of 77.8% [90]. A potential advantage of SPECT/CT is that grading the WBC uptake intensity provides a suggestion of the physiologic response of local tissue; thus, changes in intensity might be used as a prognostic tool to predict outcome of treatment [91,92]. For example, a recent study found that negative uptake on a WBC SPECT/CT was a good marker for remission of DFO and was useful in guiding the optimal duration antibiotic therapy [93]. Coupling ^{67}Ga SPECT/CT with bedside bone puncture was found to be a simple, safe and efficient procedure for the diagnosis of foot osteomyelitis in one study of diabetic patients [93]. Other advantages are that ^{67}Ga SPECT/CT imaging and biopsy can both be carried out in an ambulatory setting, and in this study, the results were used to avoid unnecessary use of antibiotics in more than half of the cases of suspected DFO [92].

Other available nuclear medicine techniques include *in vivo* methods of labelling leukocytes, radio-labelled polyclonal immunoglobulin (Ig)G and radio-labelled antibiotics. Results of studies using these techniques have varied, and most of the methods are unavailable in many countries. ^{99m}Tc/^{111}In-labelled human IgG uptake is related to vascular permeability, not inflamed tissue, and therefore not as specific as radio-labelled leukocytes [84,94,95]. Ubiquicidin 29-41 (UBI 29-41) is an antimicrobial peptide fragment reported to be highly infection specific that has been prospectively evaluated as a radiotracer (^{99m}Tc UBI 29-41) for the diagnosis of DFO in a series of 55 patients [96]. Among 38 patients with proven DFO and 17 patients free of bone infection, the sensitivity, specificity and accuracy of the ^{99m}Tc UBI 29-41 scan, in combination with a three-phase bone scan, were all 100% [96]. This technique seems worthy of further studies.

Other imaging techniques. Fluorine-18-fluorodeoxyglucose PET, which can be combined with CT (PET/CT) to improve the differentiation between osteomyelitis and soft tissue infection, has been evaluated in the diagnosis of DFO [97–99]. This technique has excellent spatial resolution and, in comparison with labelled leukocyte bone scans, can be performed more quickly and does not require blood processing. A meta-analysis of this method reported a sensitivity of 74%, specificity of 91%, positive LR of 5.6, negative LR of 0.4 and diagnostic OR of 17 [100]. While the data on this new procedure are limited, there seems to be a place for CT combined with SPECT or PET scans when MRI is unavailable or contraindicated (e.g. in a patient with a metal implant or claustrophobia). Recently, an interdisciplinary consensus committee was tasked with developing a suggested flow chart for imaging

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Table 3. Relative merits and approximated likelihood ratios of some currently available advanced imaging techniques for diabetic foot osteomyelitis, listed in descending order of usefulness

Imaging technique	+ LR	− LR	Advantages	Limitations
MRI	3.8	0.14	Good spatial resolution, high accuracy and can assess both soft tissues and bone	Reduced performance with severe ischaemia
18F-FDG PET	5.6	0.4	Good spatial resolution	Limited availability and high cost
^{99m}Tc/^{111}In-labelled leukocytes scans	4.73/2.31	0.12/0.38	High sensitivity and moderate specificity	Requires blood handling and time consuming
^{99m}Tc or ^{67m}Ga SPECT/CT	3.0	0.18	Good spatial resolution	Limited availability
^{99m}Tc-UBI 29-41 scan	Max*	Min*	Very high predictive values	Limited clinical data
^{99m}T bone scan	1.11	0.71	Widely available	Low specificity

+ LR, positive likelihood radio; − LR, negative likelihood ratio; MRI, magnetic resonance imaging; 18F-FDG, fluorine-18-fluorodeoxyglucose; PET, positron emission tomography; SPECT/CT, single-photon emission computed tomography and computed tomography; UBI 29-41, ubiquicidin 29-41.
From References [54,55,82,84,85,96].
*Specificity = 100%.

tests for patients with a DFI [101]. They recommended that the evaluation should begin with plain radiographs, but when advanced imaging is needed, MRI is still the modality of choice, although techniques such as molecular hybrid imaging, PET/CT and SPECT/CT using various radiotracers are playing an increasing role.

While both PET and SPECT combined with CT have shown promise in the diagnosis of DFO, providing both functional and anatomic information, further studies are needed to define the optimal indications and cost benefit of these techniques (Table 3). A recent narrative review of diagnosing DFO [55] combined a literature review with the 2008 IWGDF proposed guidelines [51] to propose a two-step score-based diagnostic pathway for clinicians. The suggested approach begins with a clinical assessment of six items (from physical examination, along with erythrocyte sedimentation rate and plain X-rays) [55]. The presence of ≥4 items suggests a high probability of DFO; if <4 are found, they recommend advanced imaging techniques to further separate patients at high *versus* low probability of having DFO. While this represents a logical approach, this scoring system has not yet been validated.

Bone biopsy

Available evidence supports evaluating a bone specimen as the best available diagnostic technique for both diagnosing bone infection and providing reliable data on the responsible organisms and their antibiotic susceptibility profiles [8]. Several studies have found that soft tissue or sinus tract cultures are not sufficiently accurate in predicting bone pathogens [102–104]. A retrospective review suggested that cultures from wound swabs correlate with bone biopsy culture results in only 23% of cases [105]. Although a recent study suggested that cultures of deep wound swabs correlated well enough with osseous cultures to make them useful for assessing and targeting likely pathogens in patients with suspected DFO [106], among the 34 patients who had both types of culture results were completely the same in only 16 (47%).

Bone samples can be obtained either during a surgical intervention or by percutaneous biopsy. Obtain a specimen by going through intact, uninfected skin; going through a wound risks contamination of the specimen by soft tissue organisms. Using an 11-gauge (or smaller for phalanges) bone-cutting needle, such as Jamshidi (Perfectum Corporation, distributed by Propper and Sons, or CareFusion), Ostycut (Bard Products, distributed by Angiomed) or T-lok (Angiotech), it is possible to obtain a sample of bone large enough to send one part for microbiological culture and another part for histopathological examination (Figure 1). Histological examination of bone specimens may be helpful in interpreting the results of culture, especially in case of a negative culture or one growing only commensal skin flora (e.g. coagulase-negative staphylococci, *Propionibacterium* spp., corynebacteria). Any properly trained physician can perform a percutaneous bone biopsy; it can usually be carried out at the bedside (for simple cases with a relatively large area of bone infection) or in the radiology suite (when imaging is needed to localize the involved bone). Anaesthesia is often not required because most affected patients have sensory neuropathy. Complications, such as minimal bleeding (≤3%), introducing bacteria into bone or inducing a fracture or acute Charcot arthropathy, are extremely rare [93,102,107–109].

Ideally, the bone specimen should be processed for both culture and histopathology. Infected bone usually has inflammatory cells (granulocytes early and mononuclear cells later), while the histomorphology of uninfected bone is normal in diabetic patients, including those with neuropathy or peripheral arterial disease [110,111]. Work by one group has suggested that histopathology

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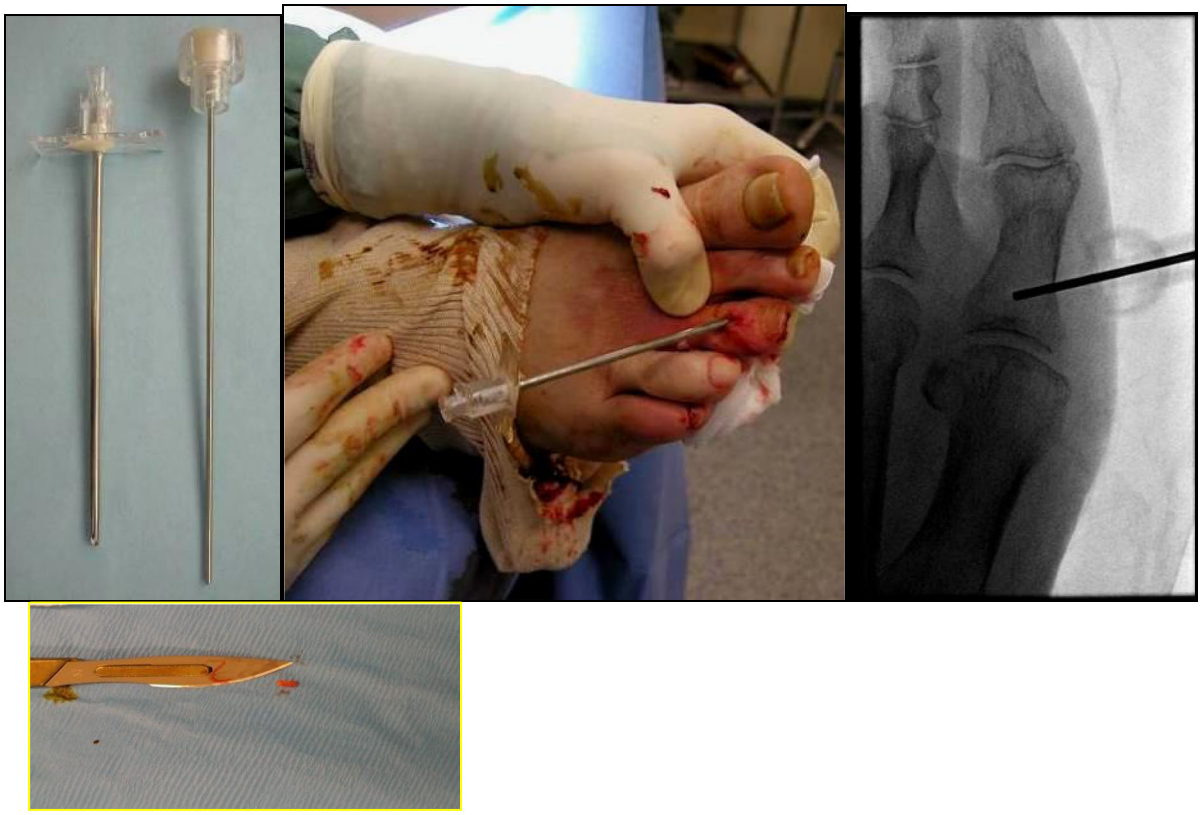

Figure 1. Technique of percutaneous bone biopsy of the foot. This may be carried out at bedside, in a radiology suite or in the operating theatre. If needed, this can be performed using fluoroscopic or computed tomographic guidance. If bone core is obtained, send to microbiology for aseptic division, with one piece for culture and the other sent to histopathology. (Photographs courtesy of Dr E. Beltrand, Orthopedic Surgery Department, Dron Hospital, Tourcoing, France)

examination may help to define three types of DFO [112]: acute, defined by necrosis and infiltration of polymorphonuclear granulocytes in cortical and medullary sites, usually associated with congestion or thrombosis of small vessels [1]; chronic, characterized by destroyed bone and infiltration of lymphocytes, histiocytes or plasma cells; and [2] acute exacerbation of chronic osteomyelitis, with a background of chronic osteomyelitis with infiltration of polymorphonuclear granulocytes [113]. However, we need further evaluation of these findings from other groups. The concordance among several pathologists in diagnosing DFO in bone samples was found to be low in one study, but this may have been related to a lack of an agreed definition of histopathological criteria [114]. A more recent study, using an agreed DFO classification scheme that included the additional histopathological type 'fibrosis', reported a high correlation in the reading by two independent pathologists [115]. A review comparing the microbiological *versus* histopathological aspects of 44 bone specimens of patients with DFI concluded that the two methods performed similarly in identifying the presence of pedal osteomyelitis [116].

Unfortunately, both histology and culture results of bone specimens may be misleading. False-positive results caused by skin contamination can be reduced by using a dorsal route in case of a plantar ulcer and by keeping a minimal distance of 20 mm from the ulcer periphery when introducing the biopsy needle. Culture of a bone specimen may be falsely negative because of sampling errors, prior antibiotic therapy or a failure to isolate fastidious organisms. Similarly, bone histopathology may be falsely negative because of sampling error or falsely positive in patients with some non-infectious inflammatory disorders. To reduce the likelihood of false negatives, it is likely best to perform bone biopsy using fluoroscopic or CT guidance and to impose an antibiotic-free period (ideally 2 weeks, but even a couple of days may be helpful) in clinically stable patients [117]. Because DFO in the absence of substantial soft tissue infection is typically a slowly progressive disease, such an antibiotic-free interval is usually safe.

In one retrospective multicentre study, using bone culture-guided antibiotic treatment was associated with a significantly better clinical outcome than using soft tissue

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culture results [118]; this finding requires confirmation by a prospective study. A reassuring finding from a retrospective study of 41 patients with suspected DFO is that among those with a negative bone culture, only ~25% developed bone infection during a 2-year follow-up [119]. While success rates of 75% or higher have been reported with empiric treatment of DFO, it is difficult to compare the results of available published studies because of differences in the populations enrolled, in the criteria used for both diagnosis and remission of infection and in the durations of follow-up [47]. Bone culture is not always needed when DFO is suspected, but clinicians should consider this procedure when the diagnosis of osteomyelitis remains uncertain despite clinical and imaging evaluations, in cases where data from soft tissue cultures are non-informative, when the infection has failed to respond to initial empiric antibiotic therapy or when considering an antibiotic regimen with a higher potential for selecting resistant organisms (e.g. rifamp(ic)in, fluoroquinolones, fusidic acid or clindamycin) [51].

Assessing severity

11. At initial evaluation of any infected foot, obtain vital signs and appropriate blood tests, debride the wound and probe and assess the depth and extent of the infection to establish its severity (strong; low).
12. At initial evaluation, assess arterial perfusion and decide whether and when further vascular assessment or revascularization is needed (strong; low).

Rationale

Accurately assessing a diabetic foot wound usually requires first debriding any callus and necrotic tissue to fully visualize the wound. Keys to classifying a foot infection are defining at initial evaluation the depth and extent of the tissues involved, determining the adequacy of arterial perfusion and possible need for revascularization and assessing for systemic toxicity [5,29,120]. While mild infections are relatively easily treated, moderate infections may be limb threatening, and severe infections may be life threatening (Table 4A). Infection severity largely guides the choice of the empiric antibiotic regimen and its route of administration and helps to determine the need for hospitalization (Table 4B), the potential necessity and timing of foot surgery and the likelihood of amputation [5,120–122].

Severity of infection is first determined by the clinical classification scheme described previously. Other clinical features of sepsis include acute oliguria or ileus. Laboratory findings suggesting a serious infection include a plasma C-reactive protein or procalcitonin level >2 standard deviations above the upper limit of normal, uncontrolled hyperglycaemia, hyperlactaemia (>1 mmol/L),

Table 4. 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 (e.g. fascia, tendon, muscle, joint and bone)
Cellulitis	Extensive (>2 cm), distant from ulceration or rapidly progressive
Local signs	Severe inflammation or induration, crepitus, bullae, discoloration, necrosis or gangrene, ecchymoses or petechiae and new anaesthesia
General	
Presentation	Acute onset/worsening or rapidly progressive
Systemic signs	Fever, chills, hypotension, confusion and volume depletion
Laboratory tests	Leukocytosis, very high C-reactive protein or erythrocyte sedimentation rate, severe/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
Current treatment	Progression while on apparently appropriate antibiotic and supportive therapy

B – Factors suggesting hospitalization may be necessary
- Severe infection (see findings suggesting a more serious diabetic foot infection)
- Metabolic or hemodynamic instability
- Intravenous therapy needed (and not available/appropriate as outpatient)
- Diagnostic tests needed that are not available as outpatient
- Critical foot ischaemia 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

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serum creatinine increase >0.5 mg/dL (44 μmol/L), coagulation abnormalities or arterial hypoxemia [123].

A deep space infection may have deceptively few superficial signs, but clinicians should consider this possibility in a patient with: evidence of systemic toxicity; inflammation distant from the skin wound; persistent infection or elevated inflammatory markers despite apparently appropriate therapy; deterioration of previously controlled glycaemia; or, pain in a previously insensate foot [20,46,124]. The presence of foot ischaemia is of particular concern, as it can both diminish clinical findings and worsen prognosis. If in doubt, consider seeking consultation from an experienced surgeon and evaluating with ultrasound, MRI or potentially other imaging techniques.

Some 'real-world' data on the presentation and outcome are available from a prospective, multicentre observational study from France of patients hospitalized for DFI [125]. Among 291 included patients, most infections were graded as moderate, but 42% met criteria for sepsis; of note was that in eight patients, the investigators found that the infection was clearly of a higher severity than graded by the treating clinicians. Half of the patients were suspected of having accompanying osteomyelitis, and more than half had peripheral arterial disease. Despite absent foot pulses in about half of the patients, the ankle-brachial index was measured in only a third of all patients. Even though the included centres had a particular interest and expertise in diabetic foot problems, the outcome was considered unfavourable in 48% of the patients. Specifically, lower extremity amputation was performed during hospitalization in 35% and in another 19% of the 150 non-amputated patients in the year after discharge; risk factors for amputation included severity of the infection and the presence of osteomyelitis. As in other studies [126], the presence of multidrug-resistant pathogens [especially methicillin-resistant *S. aureus* (MRSA)] was not associated with more severe infection or worse outcome. These findings emphasize the severity of DFI in hospitalized patients and how often this is under-appreciated and inadequately assessed.

Microbiological considerations

13. Obtain cultures, preferably of a tissue specimen rather than a swab, of infected wounds to determine the identity of causative microorganisms and their antibiotic sensitivity (strong; high).
14. Do not obtain repeat cultures unless the patient is not clinically responding to treatment, or occasionally for infection control surveillance of resistant pathogens (strong; low).

Rationale – when to send specimens for testing

Because infection is diagnosed clinically, the purpose of microbiological sampling is to identify the likely pathogens and their antibiotic susceptibilities to enable the clinician to select the most appropriate antimicrobial therapy. Acute infection in a previously untreated patient is usually caused by aerobic Gram-positive cocci (often as a monomicrobial infection), but deep or chronic wounds often harbour polymicrobial flora, including aerobic Gram-negative and obligate anaerobic bacteria [127,128]. Skin disorders, environmental exposures and especially recent antibiotic therapy can predispose to unusual or antibiotic-resistant pathogens. Wound cultures are helpful for most DFIs but are difficult to obtain in cases of cellulitis without ulceration (where skin aspiration has limited sensitivity) and unnecessary for clinically uninfected wounds. One exception is culturing uninfected wounds when seeking evidence of colonization with highly resistant organisms to determine if isolation of an institutionalized patient is needed. Clinicians should try to stay updated on antibiotic-resistant patterns of common pathogens in their area of practice. Blood cultures are only indicated for severe infections, where there are signs of systemic manifestations of sepsis [29]. When osteomyelitis is suspected, a key consideration (discussed in the osteomyelitis section) is when to obtain a specimen of bone for culture (and histopathology).

It is usually best to obtain specimens for culture as soon after the patient presents as possible, but for patients already receiving antibiotic therapy, it is sometimes useful to discontinue that treatment (if the patient is stable) and wait a few days before sampling to avoid false-negative cultures. Repeat cultures are usually unnecessary unless the patient is not clinically responding to treatment or if the initial specimen was likely to be contaminated.

15. Send collected specimens to the microbiology laboratory promptly, in sterile transport containers, accompanied by clinical information on the type of specimen and location of the wound (strong; low).

Rationale – obtaining specimens from wounds

The results of a wound culture are useful only if the specimen is appropriately collected and processed. Although swabs of open wounds are easy to collect, several studies have clearly shown that culture results with these specimens are both less sensitive and specific than tissue specimens. Aseptically obtained deep tissue specimens usually contain only true pathogens, while cultures of superficial lesions often yield a mixture of pathogens, colonizing organisms and contaminants, and miss facultative and anaerobic organisms [127,129]. Curettage (tissue

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scraping) with a dermal curette or scalpel from the base of a debrided ulcer, punch biopsy or needle aspirate of purulent secretions, generally provides more accurate results than wound swabbing [127,130,131]. If swabs are the only available method, they should be taken only after debriding and cleaning the wound. Specimens of soft tissue or bone should be sent to the laboratory promptly, in suitable sterile transport containers, and all organisms isolated should be identified.

Laboratory testing of wound specimens

Clinicians must provide the microbiology laboratory with key clinical details associated with the sample (e.g. site and type of infection, type of specimen obtained and whether or not the patient is taking antibiotics), as these will influence the specimen processing and reporting. Unfortunately, there are no internationally agreed guidelines for laboratory processing or reporting for either tissue specimens or superficial swabs from an infected foot ulcer. Such a tissue sample or swab would generally be evaluated by one of the two distinct routes: phenotypic or genotypic testing.

Phenotypic analysis

microorganism. This can be accomplished by culture of a specimen using standard or selective growth media, along with antimicrobial sensitivity testing informed by local, national or international prescribing policies. Traditional microscopy and staining techniques, such as the Gram-stained smear [132], can provide additional organism characterization. In principle, these processes are relatively cost effective and low in complexity to perform and interpret. The organisms most often reported as causing infections include most aerobic Gram-positive cocci (e.g. staphylococci and streptococci) and Gram-negative rods (e.g. Enterobacteriaceae and *Pseudomonas aeruginosa*) and common obligate anaerobes (e.g. peptostreptococci and *Bacteroides*). Disadvantages of these techniques include the fact that they take at least a couple of days to process, miss some facultative organisms and are less useful in patients taking antibiotic therapy.

Genotypic analysis

Genotypic (molecular) analysis is a more sophisticated approach to identify pathogens, where various techniques help to define the genetic makeup of an organism or group of organisms with reference to a single, or set of, trait(s). The most commonly used methods in clinical laboratories include polymerase chain reaction [133], real-time polymerase chain reaction and sequencing technologies (Sanger or next generation) [134]. These techniques are currently more complex than phenotypic testing, but their sensitivity and specificity are considerably higher, and they can produce results within hours. Thus, they offer the opportunity to rapidly and reliably detect the presence of genetic material encoding for various features used for identification, characterization, determination of virulence and potentially antibiotic resistance of pathogens [135]. While these methods detect many more organisms than phenotypic analysis, especially obligately anaerobic and fastidious species, the clinical significance of these additional isolates is not yet clear [136].

Interpreting wound culture results

Sole or predominant bacterial species identified on culture of a good quality specimen (and seen, where available, on Gram-stained smear) are likely true pathogens. If multiple organisms are isolated, especially from superficial ulcers, it can be difficult to determine which are pathogens. Clinical microbiology services must work closely with clinicians and report results in a manner that is easily understood by the recipients. Targeting antibiotic treatment against likely colonizers (e.g. coagulase-negative staphylococci and corynebacteria) may be unnecessary. These species can, however, sometimes be true pathogens, especially if they grow repeatedly or from reliable specimens. In most centres, *S. aureus* is the most frequently isolated, and perhaps most virulent, pathogen, whether alone or in combination. Streptococci (various groups of β-haemolytic and others) are also important pathogens. Enterococci are relatively frequent isolates but usually of secondary clinical importance.

Infections requiring hospitalization are often polymicrobial and may include various types of aerobes and anaerobes [29,137]. Gram-negative bacilli (mainly Enterobacteriaceae, sometimes *P. aeruginosa*, or other Gram-negative species) are usually isolated in conjunction with Gram-positive cocci from patients with chronic or previously treated infections; they are often, but not always, true pathogens. Many recent studies have reported that Gram-negative organisms (especially *P. aeruginosa*) are the most frequent isolates in DFIs occurring in patients in warm climates, especially in Asia and Africa [138–141]. It is unclear if this is related to environmental factors, footwear, personal hygiene, antimicrobial pre-treatment or other factors. Obligate anaerobic species are most frequently isolated from ischaemic or necrotic wounds or those that involve deep tissues; they are rarely the sole pathogen and most often are part of a mixed infection with aerobes [142].

Multidrug-resistant organisms, especially MRSA, are more often isolated from patients who have recently received antibiotic therapy, who have been previously hospitalized or reside in a chronic care facility or who have had a previous amputation [143,144]. After the prevalence of MRSA dramatically increased in many countries starting in the late 1990s, it has recently begun

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to decline in most countries, concomitant with improved hospital infection control measures [145–147]. DFIs caused by MRSA have been thought to be associated with more severe infections, but a recent review found that they had a similar clinical presentation and outcomes to other pathogens [126]. The previously useful distinction of community-acquired (less likely to be resistant to other antibiotics and often more virulent) *versus* healthcare-associated MRSA strains has become less reliable in recent years. In the past decade, other multidrug-resistant organisms, especially Gram-negatives with extended-spectrum β-lactamases [148,149], and even carbapenamases [150,151], have been reported to cause DFIs. Vancomycin-resistant enterococci are occasionally recovered from infections of the foot in persons with diabetes but are rarely a clinically significant pathogen. Most cases of infection with the very rare, but truly dreaded superbug, vancomycin-resistant *S. aureus* have been from patients with DFIs [152,153].

Treatment

Surgical

16. Consult a surgical specialist in selected cases of DFIs that are moderate and in all cases that are severe (weak; low).
17. Performing urgent surgical intervention is necessary in most cases of deep abscesses, compartment syndrome and virtually all necrotizing soft tissue infections (strong; low).
18. Considering surgical intervention is usually advisable in cases of osteomyelitis accompanied by spreading soft tissue infection, destroyed soft tissue envelope, progressive bone destruction on X-ray or bone protruding through the ulcer (strong; low).

Rationale

Surgery is the cornerstone of treating many deep soft tissue infections [124], and early intervention may be associated with better outcomes [46,154–156]. Emergent surgery, however, is only needed in specific circumstances, such as gas gangrene or necrotizing fasciitis, compartment syndrome or systemic sepsis. The treating clinician should consider the need for surgery in every infection, which may range from minor debridement or drainage to extensive resections, revascularization or major amputation. When the wound has a dry eschar, especially in an ischemic foot, it is often best to avoid debriding the necrotic tissue; often, these will resolve with autoamputation. Major amputation should, and usually can, be avoided unless the limb is non-viable, affected by a potentially life-threatening infection (e.g. gas gangrene or necrotizing fasciitis) or is functionally useless. Revascularization (either endovascular or open bypass) may be needed for a severely ischaemic infected limb. In many non-urgent infections, the initial surgical intervention should be limited to incision and drainage, with further resection needed only if the patient is not responding.

Figure 2 shows an algorithmic overview of the approach to treating a patient with diabetes and a foot infection. Operative treatment of a DFI should be carried out by a surgeon with thorough knowledge of the anatomy of the foot and the ways in which infection spreads through its fascial planes (Figures 3 and 4) [46,157]. The aim of surgical treatment is to drain any deep pus and to minimize tissue necrosis by decompressing foot compartments and removing devitalized and infected tissue. There is a relationship between the point of entry of an infection and the compartment in which the infection spreads: those arising from the great toe and first metatarsal head usually spread through the medial compartment; those arising in the second, third and fourth toes and metatarsal heads spread through the central compartment; and those arising from the fifth toe and fifth metatarsal head spread through the lateral compartment [46,158]. The dorsal compartment may be involved in infections arising in web spaces or in advanced infections of a plantar ulcer, either by involving a metatarsal head or via an interosseus compartment. Acute infections often spread along the tendons, as they are the path of least resistance and run within the compartments, and infected tendons must be widely removed.

Bone resection and amputation are often necessary when there is extensive soft tissue necrosis or to provide a more functional foot. A specimen of bone should be obtained at the time of surgery for analysis by culture and histopathology. Some data suggest that if there is a 'clear margin', that is, uninfected bone by culture at the site of resection, antibiotic therapy can be safely reduced from several weeks to just days, and the rate of clinical cure is significantly higher than when the margin is culture negative [159]. Surgical procedures in the infected diabetic foot should be conducted as part of an interdisciplinary approach, as it must be accompanied by proper wound care, treatment of any co-morbid medical conditions and appropriate revascularization (when needed).

Once any necessary surgical drainage and debridement have been performed and infection is under control, the long-term function of the foot is a key issue. Patients who have undergone previous surgeries or amputations may have biomechanical consequences that can potentially result in an unstable foot or lead to a foot prone to re-ulceration. The surgeon should consider these concerns when contemplating any ablative forefoot operation and balance preservation of tissue with a transmetatarsal amputation [160].

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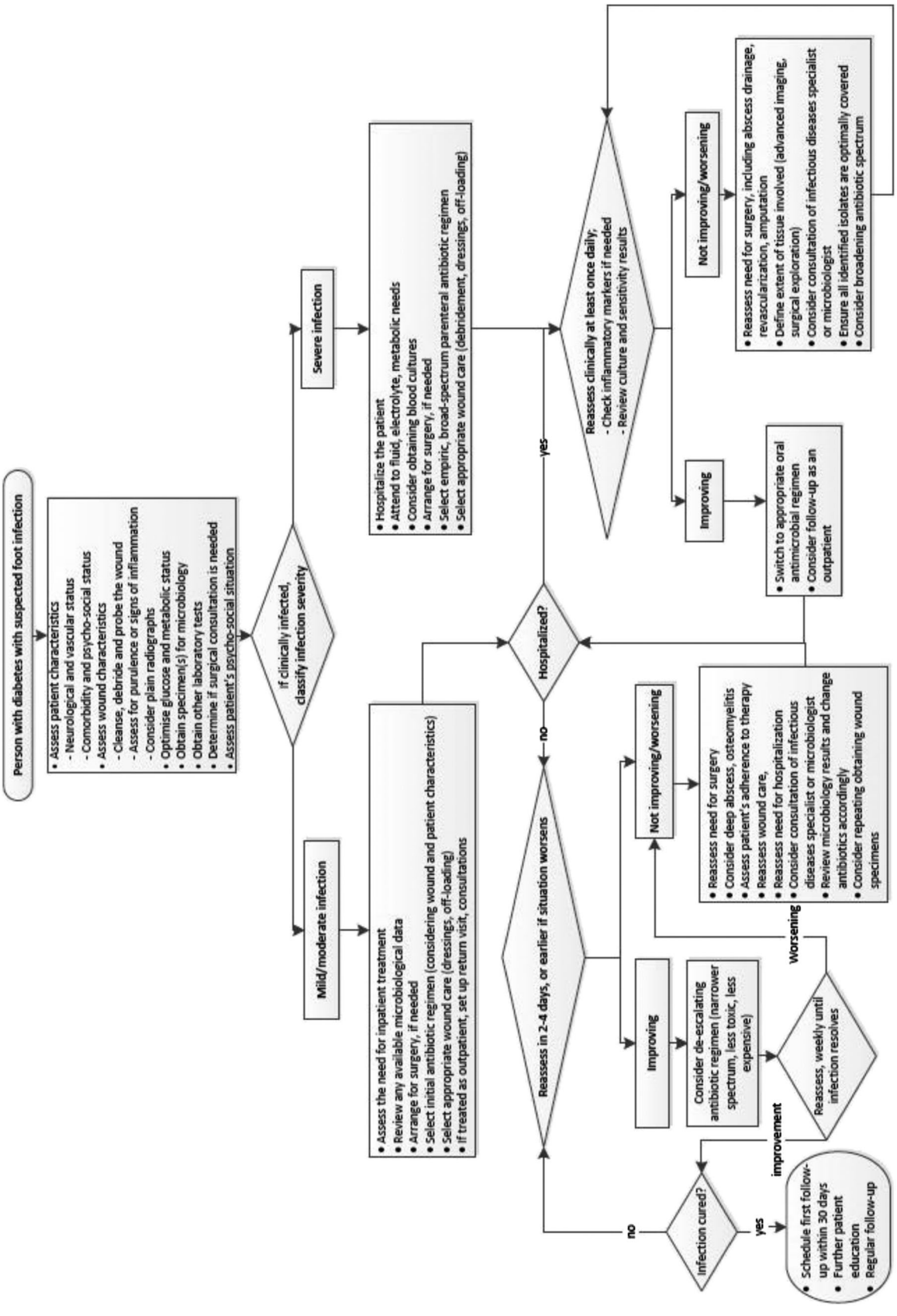

Figure 2. Algorithm overview of the approach to the patient with diabetes and a foot infection

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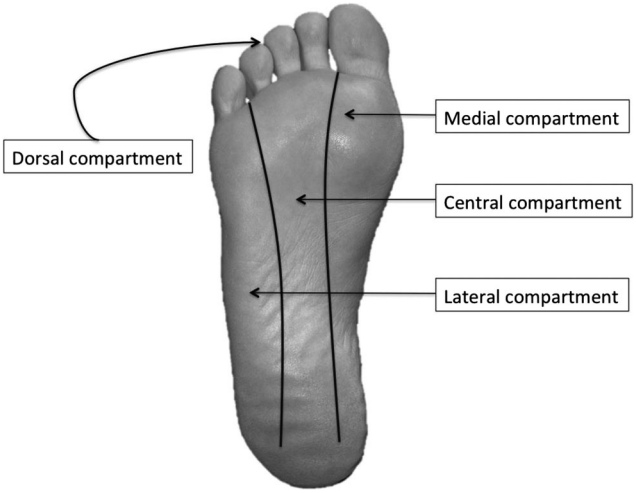

Figure 3. Longitudinal view of compartments of the foot

Antimicrobial therapy

19. While virtually all clinically infected diabetic foot wounds require antimicrobial therapy, do not treat clinically uninfected diabetic foot wounds with antimicrobial therapy (strong; low)
20. Select specific antibiotic agents for treatment based on the likely or proven causative pathogens, their antibiotic susceptibilities, the clinical severity of the infection, evidence of efficacy for DFI and costs (strong; moderate).
21. A course of antibiotic therapy of 1–2 weeks is usually adequate for most soft tissue DFIs (strong; high).

Rationale – indications for therapy

Failure to treat an infected diabetic foot wound with antimicrobial therapy is usually associated with progressive tissue destruction and poor wound healing. However, antibiotic therapy is also associated with frequent adverse effects, financial costs and increasing the risk of antibiotic resistance [143], so it should be reserved for treating wounds that are infected. Treatment with antimicrobials has not been proven to be beneficial for managing clinically uninfected skin wounds, irrespective of theoretical considerations of the bacterial 'bioburden' (a poorly defined concept) of chronic wounds [161–165]. There is no published evidence that antimicrobial therapy either accelerates wound healing or reduces the likelihood of clinical infection developing. Where the clinical assessment for the presence of infection is equivocal, the clinician must make a decision to treat the wound as either uninfected or infected (using an infection grading system) and then carefully monitor progress.

22. Administer parenteral therapy initially for most severe infections and some moderate infections, with a switch to oral therapy when the infection is responding (strong; low).

Rationale – route of therapy

For an antibiotic to reach a therapeutic concentration at the site of infection, it must first achieve an adequate serum level [166]. Because parenteral antibiotics achieve therapeutic serum levels faster and more reliably, they are recommended for patients who are systemically ill or

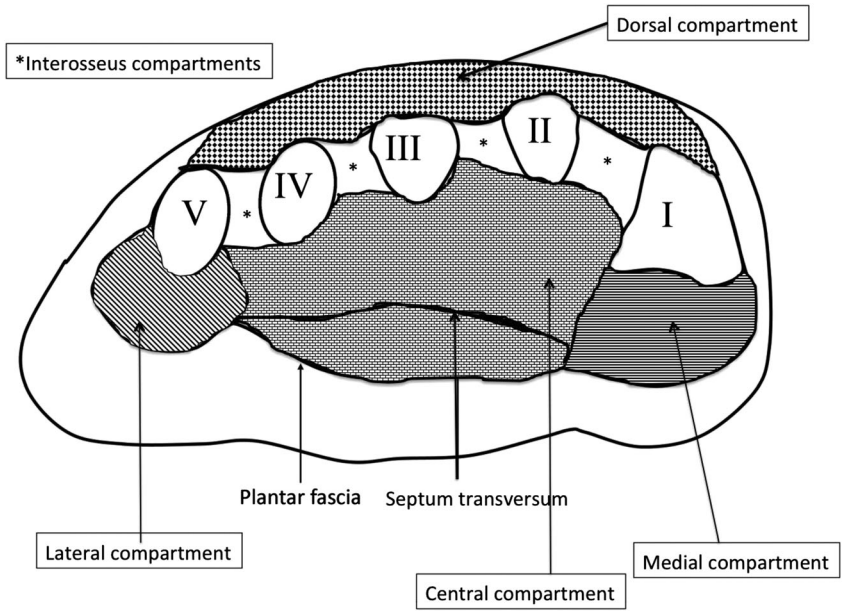

Figure 4. Transversal view of compartments of the foot

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have a severe infection. They may also be required for those unable to tolerate oral agents or who are infected with pathogens insensitive to available oral agents. After the patient's clinical condition has stabilized and the infection is responding, most can switch to oral therapy. Where available, consider outpatient intravenous antibiotic therapy for those requiring prolonged parenteral treatment, for example, for some cases of osteomyelitis or infections with organisms found resistant to available oral agents.

Compared with parenteral therapy, treatment with oral antibiotic agents is more convenient, not associated with infusion-related complications and generally less expensive. Gastrointestinal absorption of oral antibiotics (bioavailability), while variable, is excellent for several agents, such as fluoroquinolones, clindamycin, rifamp(ic)in, trimethoprim/sulfamethoxazole, linezolid and doxycycline [167]. Fluoroquinolones in particular achieve high tissue concentrations in DFIs [166,168,169], even in patients with gastroparesis [170], but most other currently used oral antibiotics also achieve adequate serum and tissue levels [167]. Unfortunately, fluoroquinolones are also associated with an increased risk of adverse effects, including *Clostridium difficile* disease, and failure with one of these agents may cause resistance to others [171]. No data are currently available to determine if adequate tissue levels predict successful clinical outcome [172]. Newly marketed agents generally have an expanded spectrum of activity, greater activity against antibiotic-resistant Gram-positive cocci, a longer half-life (allowing for less frequent dosing) or good oral bioavailability. However, they are generally considerably more expensive and have a shorter track record for safety evaluations. Virtually all comparisons of different antibiotic regimens for DFI have reported no clinically significant differences between them, and no specific agents have emerged as being preferred. One new agent, tigecycline (which has broad-spectrum activity, including against MRSA), when compared with ertapenem (with or without vancomycin) was found in a recent large, multicentre, randomized controlled trial to be significantly inferior in clinical outcomes and to have a significantly higher rate of adverse effects [173].

Peripheral vascular disease, but not diabetes *per se*, may limit the delivery, and therefore penetration, of antibiotics to infected foot tissues [170,174]. Optimally, patients with severe arterial insufficiency should undergo revascularization, but even in an ischemic limb, however, antibiotics play an important role in treating and preventing further spread of infection. Problems with limb arterial insufficiency have led some to experiment with novel methods of antibiotic delivery to the lower limb, for example, retrograde intravenous perfusion under pressure [175,176], intra-arterial (e.g. femoral) administration [177], primary closure of debrided wounds with catheter instillation of antibiotics [178] or negative pressure wound therapy (NPWT) with installation of saline, antiseptics or antibiotics [179–183]. At this time, there is insufficient evidence upon which to recommend any of these approaches.

Using topical antibiotic therapy for a foot wound is appealing, as it allows high concentrations at the site of infection without potentially toxic systemic levels [184,185]. It would also allow treatment with agents not available for systemic therapy. There are, however, some theoretical and practical caveats to its use, such as a potentially higher susceptibility to the occurrence of hypersensitivity and limited effectiveness for infection in surrounding intact tissue and possibly a lower threshold for development of antimicrobial resistance [185]. A large randomized trial of 835 patients treated for an infected DFU (most of which would meet the current PEDIS criteria for grade 2, and some grade 3) found that an investigational topical antimicrobial peptide (pexiganan) was as effective as oral therapy with a fluoroquinolone, with clinical improvement rates of 85–90% [186]. Topical antimicrobial therapy may also be used in combination with systemic antibiotic therapy. One trial compared outcomes in patients with a moderately infected DFU who were treated with standard therapy (including levofloxacin) with or without the addition of the daily application of a topical gentamicin-collagen sponge [187]. Among 56 randomized patients, the clinical cure rate for the sponge group was significantly lower at day 7 (the primary outcome) but was significantly higher at the test of cure visit (2 weeks after discontinuation of therapy, which was up to 28 days).

A limited number of marketed topical antimicrobial agents, as well as antimicrobial impregnated wound dressings (e.g. those containing various forms of silver and iodine), might be useful for preventing, or possibly even treating, mild infections [185]. Currently, supporting data are too limited to recommend topical antimicrobial therapy, but further research is warranted [185,188–191]. For deep surgical wounds, antibiotic impregnated beads, cement or biodegradable bovine collagen sponges can supply high local antibiotic concentrations (for a few days) and in some instances fill dead space [191,192]. A systematic review and an expert opinion paper concluded that the data supporting the use of gentamicin-impregnated beads are too limited to allow any recommendations [185,193].

Choice of antibiotics

Selection of an initial antibiotic regimen is usually empirical, that is, a best guess at what agent(s) will cover the likely pathogen(s). These should be selected to cover the most common infecting organisms but be modified according to infection severity and available clinical or microbiological information. We prefer relatively narrow-spectrum agents for mild infections, with adjustments if

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Table 5. Factors that may influence choices of antibiotic therapy for diabetic foot infections (specific agents, route of administration and duration of therapy)

Infection related
Clinical severity of the infection (Table 1)
History of antibiotic therapy within previous 3 months
Presence of bone infection (presumed or proven)
Pathogen related
Likelihood of non-GPC etiologic agent(s) (e.g. GNR or anaerobes)
History of colonization or infection with MDROs
Local rates of antibiotic resistance
Patient related
Allergy to any antibiotics
Impaired immunological status
Patient treatment preferences
Patient adherence to therapy
Renal or hepatic insufficiency
Impaired gastrointestinal absorption
Peripheral arterial disease in affected limb
High risk of MDROs or unusual pathogens (e.g. hospitalized patients, travel or animal exposure)
Drug related
Safety profile (frequency and severity of adverse effects)
Drug interactions potential
Frequency of dosing
Formulary availability/restrictions
Cost considerations (acquisition and administration)
Approval for indication
Likelihood of inducing *Clostridium difficile* disease or antibiotic resistance
Published efficacy data

GPC, Gram-positive cocci (aerobic); GNR, Gram-negative rods (aerobic); MDRO, multidrug-resistant organism.

clinical response is inadequate, especially if cultures disclose pathogens resistant to the selected agent(s). Initial regimens for many moderate and all severe infections should be broader spectrum, and treatment must be delivered promptly. An empirical regimen must also consider factors related to the current infection, the likely pathogen(s), the patient co-morbidities and potential drug-related issues (Table 5).

A Gram-stained smear of a wound specimen may help direct empiric antibiotic therapy by informing the clinician of the number and Gram-types of pathogens present [194]. This simple and inexpensive procedure is particularly useful in regions of limited resources. A recent study from Tanzania found that among 128 diabetic patients with a limb ulcer, the positive predictive value of a Gram-stain for bacterial growth was 93%, and the predictive value was 75% (15/20) for Gram-positive organisms and 82% (31/38) for Gram-negative organisms [132].

An empiric regimen should virtually always include an antibiotic usually active against standard strains of staphylococci and streptococci. Consider adding an agent active against MRSA if there is substantial risk of infection with this organism (e.g. a high local prevalence of MRSA, a patient with a recent stay in a healthcare institution, recent antibiotic therapy or known MRSA colonization). Patients who have been previously treated with an antibiotic (for whatever reason), or who have a more severe infection, may need extended coverage for common Gram-negative bacilli and perhaps in rare cases for *Enterococcus* species. Empiric anti-pseudomonal therapy is usually not required unless risk factors for *Pseudomonas* infection are present, for example, high local prevalence of *Pseudomonas* infections, warm climate or frequent exposure of the foot to water. Empiric anti-anaerobic therapy is appropriate for necrotic, gangrenous or foul-smelling wounds, which also require debridement. Combination therapy may be appropriate for infections presumed (or proven) to be caused by more than one organism, when the pathogen has a high potential for developing resistance (e.g. *Pseudomonas*) or when selecting an agent (e.g. rifampi(ci)n when treating osteomyelitis) to which resistance may quickly develop when used alone. Some DFI pathogens are highly resistant to antibiotics, such as those reported from Italy caused by extensively resistant *P. aeruginosa* that required treatment with colistin combined with rifamp(ci)in and imipenem [195].

When culture and sensitivity results are available, consider changing to a more specific regimen that targets just the isolated pathogens. To reduce the likelihood of antibiotic resistance, narrower-spectrum agents are preferable, but it is important to assess how the infection has responded to the empirical regimen. If the infection is improving and the patient is tolerating therapy, there may be no reason to change, even if some or all of the isolated organisms are resistant to the agents prescribed [196,197]. If the infection is not responding, however, modify treatment to cover all isolated organisms. When the infection is worsening despite the isolated bacteria being susceptible to the selected regimen, consider if surgical intervention is needed, fastidious infecting organisms were not recovered on culture, patient adherence to the treatment regimen has been suboptimal and serum levels of the prescribed antibiotic are inadequate because of decreased intestinal absorption or drug interactions causing more rapid metabolism of the antibiotic.

Several antibiotic agents have been used successfully (including some for decades) to treat DFIs despite not having been evaluated in prospective comparative studies; these include semisynthetic penicillinase-resistant penicillins (e.g. dicloxacillin, nafcillin and flucloxacillin), cephalosporins (e.g. cefazolin, ceftriaxone and ceftazidime), glycopeptides (teicoplanin, oritavancin, telavancin and dalbavancin), rifampi(ci)n, fusidic acid, trimethoprim/sulfamethoxazole and doxycycline. The following agents have demonstrated clinical effectiveness, alone or in combination, in published prospective studies that include patients with DFIs (Table 6) [7,8]:

- cephalosporins (cephalexin orally; cefoxitin, ceftizoxime, ceftibiprole and ceftaroline [198] parenterally);

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Table 6. Selecting an empiric antibiotic regimen for diabetic foot infections

Infection severity	Additional factors	Usual pathogen(s)	Potential empirical regimens[a]
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; FQ
Moderate and severe[b]			
	No complicating features	GPC ± GNR	ß-L-ase 1; second/third gen ceph
	Recent antibiotics	GPC ± GNR	ß-L-ase 2; third gen ceph, group 1 carbapenem (depends on prior therapy; seek advice)
	Macerated ulcer and warm climate	GNR, including *Pseudomonas*	ß-L-ase 2; S-S pen + ceftazidime, S-S pen + cipro, group 2 carbapenem
	Ischemic limb/necrosis/gas forming	GPC ± GNR ± anaerobes	ß-L-ase 1 or 2; group 1 or 2 carbapenem; second/third gen ceph + clindamycin or metronidazole
	MRSA risk factors	MRSA	Consider addition of, or substituting with, glycopeptides; linezolid; daptomycin; fusidic acid; T/S (±rif)*; doxycycline; FQ
	Risk factors for resistant GNR	ESBL	Carbapenems, FQ, aminoglycoside and colistin

GPC, Gram-positive cocci (staphylococci and streptococci); GNR, Gram-negative rod; MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum ß-lactamase-producing organism; S-S pen, semisynthetic penicillinase-resistant penicillin; 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; group 1 carbapenem, ertapenem; group 2 carbapenem, imipenem, meropenem, doripenem; ceph, cephalosporin; gen, generation; Pip/tazo, piperacillin/tazobactam; FQ, fluoroquinolone with good activity against aerobic Gram-positive cocci (e.g. levofloxacin or moxifloxacin); cipro, antipseudomonal fluoroquinolone, for example, ciprofloxacin; T/S, trimethoprim/sulfamethoxazole; T/S (±rif), trimethoprim/sulfamethoxazole with or without rifamp(ic)in.

*Rifamp(ic)in [270] (for now, we think that rifamp(ic)in should only be used for osteomyelitis).

[a]Given at usual recommended doses for serious infections. Modify doses or agents selected for azotaemia, liver dysfunction and so on. Recommendations based upon theoretical considerations and available clinical trials.

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

- penicillin/β-lactamase inhibitor combinations (amoxicillin/clavulanate orally; ampicillin/sulbactam, piperacillin/tazobactam and ticarcillin/clavulanate parenterally);
- carbapenems (imipenem/cilastatin and ertapenem parenterally);
- fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin, all of which can be administered orally or parenterally); and
- other agents: clindamycin (orally and parenterally), linezolid (orally and parenterally), daptomycin (parenterally), tigecycline (parenterally) and vancomycin (parenterally).

Other agents in the same antibiotic classes as those listed in Table 6 are also likely to be effective. Overall, the clinical and microbiological response rates have been similar in published trials with various antibiotics, and there is no one preferred agent or combination [7,29,51,172,199–201]. Understanding the principles of antibiotic therapy is more important than knowing the specific agents currently in favour, especially as new antibiotics are introduced and some older ones are made obsolete by emergence of resistance or newly appreciated toxicities or adverse interactions [194,200,202,203]. In the absence of a compelling reason to choose a specific antibiotic, the one with the lowest acquisition cost is preferred, even though antibiotics account for only a small portion of the treatment costs for a foot infection [204]. There is an urgent need for comparative trials and economic analyses of various anti-infective regimens for DFIs [7,29,205,206]. Suggested empirical antibiotic regimens, by type of infection, are given in Table 6. Fungi are occasional pathogens in DFI, most often as part of a mixed infection [207].

Another factor that appears to impair response to antibiotic therapy in DFI is the presence of biofilm. These slime-enclosed aggregates of sessile bacteria adhering to surfaces are present in many chronic infections, and the majority of DFIs, and demonstrate great resistance to most antibacterial agents as well as to host defences [208,209]. Eradicating bacteria in a biofilm usually requires physical removal, often combined with high doses of an antimicrobial agent found to be more active against these organisms. These include topical agents such as hypochlorous acid [210] and cadexomer iodine [211] and systemic agents such as fluoroquinolones, rifamp(ci)in, daptomycin or fosfomycin [212,213].

Duration of therapy

The optimal durations of antibiotic therapy for DFIs involving skin and soft tissue or bone are unknown. Based on data from available studies, for mild to moderate skin and soft tissue infections, 1–2 weeks is usually effective [8,130,172], while for more serious skin and soft tissue infections, 3 weeks is usually sufficient [8,172,196,197,214,215]. Antibiotic therapy can generally be discontinued when

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signs and symptoms of infection have resolved, even if the wound has not healed, as the antibiotics are employed to treat infection, not to heal wounds. More extended treatment may be needed for immunocompromised patients, for wounds that are poorly perfused, deep, large or necrotic, or for osteomyelitis (*vide infra*), but this decision should be accompanied by clinical re-evaluations to support the treatment strategy. In the occasional instances in which prolonged parenteral therapy is needed, outpatient therapy should be considered [216]. The necessary duration of therapy may be shortened by adequate debridement, resection or amputation of infected tissue. Some patients who cannot (or refuse to) undergo surgical resection, or who have an implanted foreign body at the infection site, may require prolonged or intermittent suppressive antibiotic therapy.

Wound care

23. Do not select a specific type of dressing for a DFI with the aim of preventing an infection, or improving its outcome (strong; high).

Rationale

For treating DFIs, antibiotics (and often surgery) are necessary but not sufficient to overcome inadequate vascular supply, poor glycaemic control, persistent wound trauma or improper wound care [217,218]. Most DFUs need to be carefully cleaned and debrided to remove devitalized tissue that may impede wound healing and foster infection. No prospective studies have evaluated the optimal frequency or type of debridement for diabetic foot ulcers, but *post hoc* evaluations of clinical studies in non-infected DFUs suggest that more frequent debridement is associated with a higher healing rate [219,220]. Systematic reviews of various wound dressings and topical antimicrobials have found no evidence that any specific type of therapy is better than others [221,222]. For example, simple gauze dressings have performed as well for healing DFUs as silver dressings, hydrogels, alginates and foam dressings. In general, DFUs with heavy exudate need a dressing that absorbs moisture, while dry wounds need topical treatments that add moisture. Dressings should optimally be changed at least daily, both to apply a clean wound covering and to allow careful examination of the wound for infection. Applying a total contact cast makes it difficult for the clinician and patient to visualize the wound for evaluation of response to treatment between changes and is generally not appropriate for infected wounds. For further discussion of wound care, the reader is referred to the IWGDF guidance document on wound care.

Treating osteomyelitis

24. For DFO, we recommend 6 weeks of antibiotic therapy for patients who do not undergo resection of infected bone and no more than a week of antibiotic therapy if all infected bone is resected (strong; moderate).

While many cases of DFO require, or benefit from, surgical debridement or resection of bone, some can be treated successfully by medical therapy alone. Several published retrospective series have shown that DFO can be arrested (or even apparently cured) with antibiotic therapy in the absence of surgical intervention in about two thirds of cases [109,118,223–227]. In these reports, clinicians have generally employed the higher recommended daily doses of antibiotics given for at least 2 (and usually 3–6) months. Unfortunately, available studies do not provide information to inform which types of DFO cases may be successfully treated without surgery [109,118,223–227]. In some cases, limited surgery (resection of infected and necrotic bone without amputation) combined with antibiotic therapy may be most appropriate [156,228–231]. A retrospective study from four centres in France and Spain compared outcomes of patients with bone culture-proven *S. aureus* DFO who were treated by either 'medical' (just antibiotic therapy, other than soft tissue debridement at the bedside) or 'surgical' (operative treatment combined with prolonged antibiotic therapy) [232]. Outcomes were similar for the two groups (favourable in 80% in the surgical group and 87% in the medical group), but significant differences between patients in the medical group compared with the surgical group were that they were less frequently hospitalized (49% *versus* 94%), had a shorter length of hospital stay (17 *versus* 12 days), had a slightly longer course of antibiotic therapy (11 *versus* 10 weeks) and had more treatment-related side effects (33% *versus* 9%).

Recently, the first prospective, randomized trial was published that compared the outcomes of the treatment of DFO in patients who received exclusively antibiotic therapy (for up to 90 days) *versus* those who underwent limited resection of the osteomyelitic bone (accompanied by ~10 days of antibiotic therapy) [233]. The primary end point was foot wound healing, which occurred in 18 antibiotic-treated patients compared with 19 predominantly surgically treated patients (75% *versus* 86.3% healing rates, respectively, $p = 0.33$). There was no significant difference in median time to healing (6–7 weeks), the need for surgery (first or repeat procedure, including minor amputations), re-ulceration (up to 12 weeks after healing) or treatment-related complications. This study suggests that the short-term results of therapy with either antibiotics alone or predominantly

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Table 7. Factors potentially favouring selecting either primarily antibiotic or surgical resection for diabetic foot osteomyelitis

Medical
Patient is too medically unstable for surgery
Poor postoperative mechanics of foot likely (e.g. with midfoot or hindfoot infection)
No other surgical procedures on foot are needed
Infection is confined to small, forefoot lesion
No adequately skilled surgeon is available
Surgery costs are prohibitive for the patient
Patient has a strong preference to avoid surgery
Surgical
Foot infection is associated with substantial bone necrosis or exposed joint
Foot appears to be functionally nonsalvageable
Patient is already nonambulatory
Patient is at particularly high risk for antibiotic-related problems
Infecting pathogen is resistant to available antibiotics
Limb has uncorrectable ischaemia (precluding systemic antibiotic delivery)
Patient has a strong preference for surgical treatment

Modified from Lipsky, 2014, *Diabetes Care* [234].

surgical treatment (with some antibiotic therapy) are similar in patients who have neuropathic forefoot ulcers complicated by osteomyelitis, but without ischaemia or necrotizing soft tissue infections. Noteworthy aspects of this trial were that the number of enrolled patients was relatively small, only about a third of the patients that they evaluated for the study were eligible for inclusion and the duration of follow-up was rather short [234]. Table 7 summarizes factors potentially favouring selecting either primarily antibiotic or surgical treatment for DFO.

The IWGDF produced a full systematic review of, and proposed guidelines for, the treatment of DFO in 2008 [51] and updated the review for all types of DFI in 2012 and 2015 [8,172]. Recently, a non-systematic review provided guidance on selecting systemic antibiotic therapy for chronic osteomyelitis [235]. Among the important factors to consider when treating osteomyelitis are the following: the anatomic site of infection, the local vascular supply, the extent of both soft tissue and bone destruction, the presence of any systemic signs of infection and the patient's preferences for treatment. The choice of an antimicrobial agent for treating osteomyelitis should optimally be based on the results of a bone culture, especially because of the need for long-duration therapy [48,118]. If empiric therapy is necessary, the regimen should usually cover *S. aureus* as it is the most common pathogen, but the patient's history or culture results may suggest a need for broader coverage. Some antibiotics may not penetrate well into infected bone, but the unreliability of measuring bone levels limits the value of published data on this issue. Furthermore, the association between high bone levels of an antibiotic and improved outcome has not yet been studied. Although treatment of osteomyelitis has traditionally been parenteral (at least initially) and prolonged (at least 4 weeks), these recommendations are not based on strong data. Many patients can probably be switched to oral therapy after about a week of parenteral treatment to complete their treatment course. Any oral antibiotics selected should have good bioavailability [e.g. fluoroquinolones, rifampi(ci)n (always combined with another agent), clindamycin, linezolid, fusidic acid or trimethoprim–sulfamethoxazole]. If all of the infected bone is surgically removed, a shorter course of antibiotic therapy (i.e. 2–14 days) may be sufficient, depending on the status of the soft tissues [8]. Extending post-debridement antibiotic therapy beyond 6 weeks, or giving IV treatment longer than 1 week, does not appear to increase the remission rate. A recent randomized controlled trial that compared 6 *versus* 12 weeks of antibiotic therapy for non-surgically treated DFO in 40 patients found no significant difference in the remission rate (60% *versus* 70%) but significantly fewer adverse effects with the shorter treatment [236,237].

For some patients with apparently incurable infection, long-term suppressive therapy, or intermittent short courses of treatment for recrudescent symptoms, may be the most appropriate approach. When there are clinical signs of persistent or recurrent infection, the clinician should strongly consider a percutaneous bone biopsy for culture to determine if there is persistent infection or any changes in the pathogens or their antibiotic susceptibilities. Antibiotic-impregnated beads [191], sponges [187], cement or orthopaedic implants have been used successfully to treat DFO in a few small studies [192].

Adjunctive therapies

25. We suggest not using any adjunctive treatments for DFI (weak; low).

Rationale

Several studies have reported the results of additional approaches (beyond antibiotics and surgery) to help resolve infection, accelerate wound healing or improve host response. These include NPWT, systemic hyperbaric oxygen therapy (HBOT), granulocyte colony-stimulating factors and larval (maggot) therapy [8,238]. While NPWT is often used for infected cardiothoracic, traumatic and orthopaedic wounds, we know of no studies that have specifically investigated the role of NPWT to treat infected diabetic foot wounds. A randomized controlled study of patients with chronic diabetic foot wounds after partial amputation reported a non-significantly higher rate of infection in those treated with NPWT than in the controls (16.8% *versus* 9.4%) [239].

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One retrospective cohort study reported a higher proportion of healed or surgically closed wounds and shorter periods of hospitalization in infected diabetic patients treated with NPWT with simultaneous irrigation with an antiseptic solution [181]. One controlled trial of treatment of diabetic foot wounds included a group of 130 patients randomized after surgical debridement of an infected open minor amputation to either NPWT or a semi-occlusive silver dressing [240]. The authors reported that the NPWT group had a significantly 'more rapid development of granulation tissue covering exposed bone' and 'better and more rapid control of infections' and reduced time to complete close of the wound. We find it difficult to interpret these end points and await further prospective trials of this therapy for infected wounds.

Several randomized clinical trials evaluated HBOT for treating DFUs, and some have shown an increased likelihood or faster rates of wound healing and fewer major amputations [241–244]. Most of these studies included Wagner 3 ulcers, which can include patients with osteomyelitis, but none presented any subanalyses of patients with infected DFUs or specifically reported on infection-related outcome measures. To date, there are no data to support using HBOT to treat either soft tissue infection or osteomyelitis.

A meta-analysis of five studies with a total of 167 patients with DFIs found that therapy with various types of investigational granulocyte colony-stimulating factor treatments was associated with significantly fewer surgeries and amputations and shorter hospital stays but did not increase the likelihood of resolving infection, healing wounds or shortening the duration of systemic antibiotic therapy [8,245,246]. Maggot debridement, or larval biotherapy, has been shown to have antibacterial effects [247]. A recent systematic review of its value for chronic wounds, including DFUs, reported that in one study, there was a significantly longer antibiotic-free time period in patients who received maggot therapy than in those who did not, but in two studies, the proportion of antibiotic use was similar for those who did and did not receive maggot therapy [248,249].

Outcome of treatment

With appropriate treatment, the signs and symptoms of mild DFIs almost always resolve without need for amputation. When infection involves deep soft tissue structures or bone, the outcome is often less favourable; many require surgical debridement, bone resection or partial amputations. With extensive infection, or in medical centres with limited expertise or resources, lower extremity amputation rates may reach 50–60% [8,250]. For hospitalized patients, poor outcomes (mostly amputations) occur in almost half, even in expert centres [125]. A recent study from the United States found that of 57 hospitalized DFI patients who were discharged to an outpatient parenteral antibiotic therapy program, 93% were considered a treatment success on discharge, but only 64% had resolution of the DFI at 6 months of follow-up [38]. Not surprisingly, treatment success was significantly higher with moderate compared with severe infections (79% *versus* 21%, $p = 0.04$). Regrettably, in this small, retrospective study, adherence to the IDSA DFI guidelines was suboptimal and did not correlate with clinical outcome. Another recent US study found that of 234 patients with a DFI hospitalized in three different types of university-affiliated centres, only 17% of wounds healed, and the amputation rate was 42% [251]. Independent risk factors for amputation were the presence of gangrene or osteomyelitis and a wound area of >5 cm^2.

In the hands of an experienced surgeon, most amputations can be foot sparing (i.e. below the malleoli), and long-term control of infection is achieved in over 80% of cases [113]. The presence of limb or foot ischaemia has an important adverse effect on the outcome, synergizing with infection to worsen the prognosis [252]. Unfortunately, having had one foot infection is associated with an increased likelihood of another; foot infection recurs in 20–30% of diabetic patients, especially those with underlying osteomyelitis [253].

It is difficult to know when osteomyelitis is cured, but clinical experience suggests that evidence of remission includes a drop in the erythrocyte sedimentation rate (and to a lesser extent, the C-reactive protein level), reconstitution of destroyed bone on plain radiograph and healing of any overlying soft tissue wound. While not recommended for this purpose, a negative nuclear medicine scan makes active ongoing infection unlikely. A negative culture of the bone margin left after operative resection of infected bone is associated with a lower incidence of recrudescence of infection than if the bone margin is culture positive [254]. Because DFO recurrences are common, it is best to consider apparent treatment success a 'remission' for at least a year, before calling it a cure. Factors that predict healing include the absence of any exposed bone, palpable pedal pulses, blood pressure in the toe of >45 mmHg or in the ankle of >80 mmHg, peripheral white blood cell count of $<12\,000/\text{mm}^3$ and a lower extremity transcutaneous oxygen tension of >40 mmHg [12,255]. There is no convincing evidence that clinical outcome is related to the specific infecting organism, even with multidrug-resistant (e.g. MRSA) strains [126], including in cases involving bone [256]. Because of the risk of reinfection, it is crucial to educate patients who have a DFI about prevention techniques and the need for prompt consultation for any future foot problems.

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Issues of particular importance in developing (low-income) countries

26. When treating a DFI, assess for use of traditional remedies and previous antibiotic use and consider local bacterial pathogens and their susceptibility profile (strong; low).

Rationale

These guidelines must, of course, be adapted to the local circumstances in which a healthcare provider sees patients. Many aspects of the management of DFIs may differ in developing (or low income), compared with more developed (higher income), countries. In resource-constrained regions, infections are often a consequence of wounds caused by the diabetic person wearing footwear that is not sufficiently protective (e.g. sandals) or poorly fitting, or wearing none at all. Poor hygiene may be associated with risk of rat bites [257] and increases the risk of ulcer infection and may enable larval infestation (myiasis) [258]. Persons with foot wounds may delay seeing a healthcare provider because they lack health-related education, nearby healthcare services or financial resources [259]. During this period of delay, the person may attempt to treat the infection with various traditional remedies, including plants or other locally accepted treatments [260–262], seek treatment from a faith or herbal healer or have to be referred from primary to district to regional health centres [263]. In a recent questionnaire study of patients with a DFI in the West Indies, 382 who had sought medical attention soon after detecting the infection were compared with 313 who voluntarily chose to delay medical therapy in favour of home remedies [264]. The home remedy group had significantly worse outcomes for duration of hospitalization (16.3 *versus* 8.5 days) and number of (and need for operative) debridements. They also had a non-significant trend toward more major amputations (9.3% *versus* 5.2%) and an estimated increase cost for their treatment of $US 10 821. Furthermore, in developing countries, people can often buy antibiotics without a prescription; thus, they may have treated themselves, occasionally with the advice of a local pharmacist or other trusted but non-licenced persons, before presenting to a physician. This unsupervised treatment, sometimes with generic drugs of questionable quality, expired medications or at inadequate doses, is likely to result in infections caused by more antibiotic-resistant organisms [260,265].

Healthcare providers in developing or low-income countries may also face a lack of access to a microbiology laboratory and so cannot determine the identity and antibiotic susceptibility of foot pathogens infecting an individual patient, or of current isolates and susceptibilities in the community. Recent studies have demonstrated substantial variations in the causative pathogens of DFIs in different regions of the world [266]. In contrast to Western countries, studies from Asia and Africa have reported that aerobic Gram-negative organisms (especially *P. aeruginosa*) are more common. Similarly, many clinicians will not have access to even basic (not to mention more sophisticated) imaging equipment or to specialist consultants with adequate knowledge of foot anatomy and the available conservative management methods for treating DFIs. Even when a patient sees a physician and receives an antibiotic prescription, indigent patients may be unable to afford the full course of therapy or may be prescribed inexpensive but potentially more toxic or less effective agents.

Adverse social situations for many patients in these regions may also impair proper treatment. Home or work circumstances may make it difficult for them to stay off the affected foot or to afford or be able to purchase or use an off-loading device. Furthermore, they may have travelled a long distance to see a physician and cannot easily return for follow-up visits. Understandably, patients and providers in low-income countries do not want 'second-class', or 'best we can afford', medical care. Improving management of DFIs in developing countries will likely require a combination of education (for patients, pharmacists and healthcare providers) and funding (for diagnostic, therapeutic and preventative services) [261,267,268].

Key controversies

1. How should we monitor treatment 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 osteomyelitis?

Because bone infection is more difficult to cure than just soft tissue involvement, and the duration of antibiotic therapy is more prolonged for osteomyelitis than soft tissue infection, this is a key issue.

3. How should we adapt approaches to DFI management in low-income countries?

The rise in incidence of DFIs in some of these countries is steep and with their constrained resources, finding optimal approaches, without recommending 'second-class' care, is crucial to improve outcomes.

4. When, and which, imaging studies should we order for a patient with a DFI?

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Imaging studies can be expensive and time consuming, and awaiting their results may delay appropriate therapy. Especially with the advent of new technologies, evaluating their cost effectiveness to optimize use would improve management.

5. When should we select primarily medical *versus* surgical treatment for osteomyelitis?

This has been a controversial and simmering issue for some time, addressed by several retrospective studies but to date only one prospective one. An additional large, well-designed prospective study could largely answer the question.

6. Is there a definition 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 know which to employ.

7. What is the value and proper interpretation of molecular (genotypic) microbiological testing for DFI?

The era of molecular microbiology is inexorably approaching, but it is crucial for clinicians to understand when to order, and how to interpret the results of, these tests in deciding on antibiotic therapy.

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