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REVIEW ARTICLE

Expert opinion on the management of infections in the diabetic foot

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Summary

This update of the International Working Group on the Diabetic Foot incorporates some information from a related review of diabetic foot osteomyelitis (DFO) and a systematic review of the management of infection of the diabetic foot. The pathophysiology of these infections is now well understood, and there is a validated system for classifying the severity of infections based on their clinical findings. Diagnosing osteomyelitis remains difficult, but several recent publications have clarified the role of clinical, laboratory and imaging tests. Magnetic resonance imaging has emerged as the most accurate means of diagnosing bone infection, but bone biopsy for culture and histopathology remains the criterion standard. Determining the organisms responsible for a diabetic foot infection via culture of appropriately collected tissue specimens enables clinicians to make optimal antibiotic choices based on culture and sensitivity results. In addition to culture-directed antibiotic therapy, most infections require some surgical intervention, ranging from minor debridement to major resection, amputation or revascularization. Clinicians must also provide proper wound care to ensure healing of the wound. Various adjunctive therapies may benefit some patients, but the data supporting them are weak. If properly treated, most diabetic foot infections can be cured. Providers practising in developing countries, and their patients, face especially challenging situations. Copyright © 2012 John Wiley & Sons, Ltd.

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Introduction

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 2004 [1], incorporating some information from a related IWGDF 2008 publication on osteomyelitis [2] and from the concurrently published 'Systematic Review of the Effectiveness of Interventions in the Management of Infection in the Diabetic Foot' [3]. Our intention is to present a brief overview to assist clinicians worldwide in diagnosing and treating foot infections in persons with diabetes. Separately, we have proposed 'Specific Guidelines on the Management of Diabetic Foot Infections', also published concurrently in this journal.

The development of a foot infection is associated with substantial morbidity, including discomfort, healthcare provider visits, antibiotic therapy, wound care and often surgical procedures. Furthermore, foot infection is now the most frequent diabetic complication requiring hospitalization and the most common precipitating event leading to lower extremity amputation [4–6]. Managing infection requires careful attention to properly diagnosing the condition,

obtaining specimens for culture, selecting empirical and definitive antimicrobial therapy, determining when surgical interventions are needed and caring for the wound. A systematic and, to the extent possible, evidence-based approach to diabetic foot infections (DFIs) should result in better outcomes.

Pathophysiology

In persons with diabetes, foot infection is a common problem. Infection is best defined as invasion and multiplication of microorganisms in host tissues that induces a host inflammatory response, usually followed by tissue destruction. DFI is defined clinically as a soft tissue or bone infection anywhere below the malleoli. These infections usually occur in a site of skin trauma or ulceration [7]. Peripheral neuropathy is the main factor leading to skin breaks and ulcerations, which then become colonized with skin flora and ultimately infected. Foot ischemia, 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 ischemia increases the risk of a wound becoming infected [8] and adversely affects the outcome of infection [9]. Factors that predispose to foot infection include having a wound that is deep, long-standing or recurrent, ill-defined diabetes-related immunological perturbations and chronic renal failure [8,10,11]. 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. When infection-induced pressure in a compartment exceeds capillary pressure, ischemic necrosis may ensue [12,13]. Systemic symptoms (e.g. feverishness, chills), marked leukocytosis or major metabolic disturbances are uncommon in patients with a DFI, but their presence denotes a more severe, potentially limb (or even life) threatening infection [14,15]. If not diagnosed and properly treated, DFIs tend to progress, sometimes rapidly.

Classification

The clinician must first diagnose the presence of a DFI and then should classify the infection's severity. Over the past three decades, investigators 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. While several include the presence or absence of 'infection' (rarely defined), only two (nearly identical) schemes proposed by the Infectious Diseases Society of America and the IWGDF (Table 1) describe how to define both the presence and severity of infection [16].

Diagnosis

Soft tissue infection

Because all skin wounds harbour microorganisms, their mere presence, even if they are virulent species, cannot

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 International Working Group on the Diabetic Foot (IWGDF)

Clinical classification of infection (IDSA), with definitions	IWGDF grade (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 $>0.5\,cm^1$ around the ulcer •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, venous stasis)	
– Infection involving the skin or subcutaneous tissue only (without involvement of deeper tissues and without systemic signs as described below) – Any erythema present extends $<2\,cm^1$ around the wound – No systemic signs or symptoms of infection (see below)	2 (mild infection)
– Infection involving structures deeper than skin and subcutaneous tissues (e.g. bone, joint, tendon) or erythema extending $>2\,cm^1$ from the wound margin – No systemic signs or symptoms of infection (see below)	3 (moderate infection)
– Any foot infection with the following signs of a systemic inflammatory response syndrome, as manifested by ≥ 2 of the following: •Temperature >38 or $<36\,^{\circ}C$ •Heart rate >90 beats/min •Respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg •White blood cell count $>12\,000$ or <4000 cu/mm or 10% immature (band) forms	4 (severe infection)

[1]In any direction.

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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 the basis for diagnosing infection [17], but no convincing data support this concept in the diabetic foot; furthermore, quantitative microbiology is rarely available outside of research laboratories. Thus, DFI must be diagnosed clinically (Table 1), with wound cultures reserved for determining the causative organisms and their antibiotic sensitivities. Clinical diagnosis rests on the presence of at least two local findings of inflammation, that is, redness (erythema or rubour), warmth (calour), pain or tenderness (dolour), induration (swelling or tumour) or purulent secretions [16]. 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 [18]. These may be helpful when local and systemic inflammatory signs are diminished because of peripheral neuropathy or ischemia [19–21]. Because infection can worsen quickly, the diagnosis should be pursued methodically [19] and aggressively [22]. 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

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 (inflammatory cells, necrosis) and the isolation of bacteria from an aseptically obtained bone sample [2]. Because these procedures 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 associated abscess and soft tissue involvement, the causative organism(s) and the adequacy of limb perfusion. The main problems in diagnosing osteomyelitis are the delay in detecting bony changes in early infection on plain radiographs and the difficulty in distinguishing bony changes caused by infection from those related to Charcot neuro-osteoarthropathy (CN) on most imaging studies. As will be discussed, analyses from recent expert publications [2,23] and systematic reviews [2,24,25] provide guidance on the best diagnostic studies.

Clinical evaluation

Clinicians should suspect osteomyelitis when an ulcer overlying a bony prominence fails to heal despite adequate off-loading or when a toe is erythematous and indurated. The likelihood ratio (LR) of a clinician's suspicion of osteomyelitis is surprisingly good: positive LR 5.5 and negative LR 0.54 [24,25]. 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 than smaller ones [24–27]. Osteomyelitis can, however, occur in the absence of overlying local signs of inflammation [26].

Probe-to-bone test

This is a useful clinical diagnostic tool. Striking bone (detected by the hard, gritty feel) with a blunt sterile metal probe gently inserted through a wound increases the likelihood that the patient has osteomyelitis if the prevalence of bone infection is high (i.e. >60%) in the population under scrutiny [28,29]. Conversely, a negative probe-to-bone test in a patient at low risk (i.e. ≤20%) essentially rules out osteomyelitis [30–32].

Blood tests

The erythrocyte sedimentation rate is diagnostically useful; when elevated (usually defined as >70 mm/h), it increases the likelihood of osteomyelitis underlying a diabetic foot wound (positive LR 11), while lower levels reduce the likelihood (negative LR of 0.34) [24,26,33,34]. Based on fewer data, an elevated C-reactive protein, procalcitonin or blood leukocyte count may also be predictive of the presence of osteomyelitis [34,35].

Imaging studies

Plain radiography. Characteristic features of osteomyelitis on plain X-rays of the foot (usually two or three views) are summarized in Table 2 [26,36–38]. Among the many studies that have assessed the accuracy of plain radiography in diagnosing osteomyelitis [26,36,38–53], nine were prospective in design [26,36,38–41,44,45,52]. Overall, the

Table 2. Common imaging features of diabetic foot osteomyelitis

Plain radiographs
•Periosteal reaction or elevation •Loss of cortex with bony erosion •Focal loss of trabecular pattern or marrow radiolucency •New bone formation •Bone sclerosis with or without erosion •Sequestrum: devitalized bone with radiodense appearance that has become separated from normal bone •Involucrum: a layer of new bone growth outside existing bone resulting from the stripping off of the periosteum and new bone growing from the periosteum •Cloacae: opening in involucrum or cortex through which sequestra or granulation tissue may be discharged
Magnetic resonance imaging
•Low focal signal intensity on T1-weighted images •High focal signal on T2-weighted images •High bone marrow signal in short tau inversion recovery (STIR) sequences •Less specific or secondary changes: ○Cortical disruption ○Adjacent cutaneous ulcer ○Soft tissue mass ○Sinus tract formation ○Adjacent soft tissue inflammation or oedema For both modalities, bony changes are often accompanied by contiguous soft tissue swelling.

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sensitivity varied from 28% to 75%. The timing of the imaging greatly influences its usefulness, as longer-standing cases are more likely to show bony abnormalities on plain radiographs than those present for less than a couple of weeks. In the systematic review by Dinh *et al.* [25], the pooled sensitivity of the four eligible studies was 0.54 and the pooled specificity was 0.68, with a diagnostic odds ratio of 2.84 and a *Q* statistic of 0.60 [26,36,38,52]. In the systematic review by Butalia *et al.* [24], analysing seven studies of plain radiographs, the summary positive likelihood ratio was 2.3 [95% confidence intervals (CI) 1.6–3.3], while the negative likelihood ratio was 0.63 (95% CI 0.5–0.8) [26,36,38,43,47,48,50]. These results suggest that radiographic findings are only marginally predictive of osteomyelitis if positive and even less predictive of the absence of osteomyelitis if negative. Of note is that neither review identified a study that obtained sequential plain radiographs of the foot over time. *Changes* in radiological appearance over an interval of at least 2 weeks are more likely to predict the presence of osteomyelitis than a single study, although correctly targeted antibiotic therapy may prevent these changes.

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 [16]. The key features suggestive of osteomyelitis on MRI are listed in Table 2. In their meta-analysis, Dinh *et al.* [25] identified four trials using MRI, all of which were prospective [27,36,38,54] and two of which used a consecutive recruitment method [36,38], but only one was conducted within the past 10 years [27]. The prevalence of osteomyelitis in the four studies ranged from 44% to 86%. The pooled sensitivity of MRI for diabetic foot osteomyelitis (DFO) was 0.90 (CI 0.82–0.95), and the diagnostic odds ratio was 24.4. In 16 trials identified in the meta-analysis by Kapoor *et al.* [55], 9 were prospective studies and 11 included only subjects with diabetes, although enrolment criteria were quite varied. The prevalence of standard defined osteomyelitis was 50% (range 32% to 89%), the pooled sensitivity was 77–100% and the specificity was 40–100%. In subjects with diabetes, the diagnostic odds ratio was 42 (CI 15–120), the summary positive likelihood ratio was 3.8 (CI 0.2.5–5.8) and the summary negative likelihood ratio was 0.14 (CI 0.08–0.26) [27,36,38,41,45,49,51,56–64]. More recently performed studies reported lower diagnostic odds ratios (25, CI 6–117) compared with older ones, perhaps because their study designs were better. The subgroups of patients with other diagnoses (e.g. CN) were too small to analyse any differences among the studies.

Nuclear medicine. Three recent meta-analyses reviewed nuclear medicine techniques for evaluating the diabetic foot [25,55,65]. Capriotti *et al.* reviewed 57 papers, including seven reviews on the clinical value of several nuclear medicine methods [65]. Among the several types of nuclear imaging scans, a bone scan, usually performed with ^{99m}Tc-methylene diphosphate and done in time-sequence phases, is considered suggestive of osteomyelitis when it discloses increased blood-pool activity and radionuclide intensity localized to the bone [25]. Three-phase bone scans are sensitive (90%), but not specific (46%) [65], with a calculated summary negative predictive value of 71% and positive predictive value of 65%. Among six studies with 185 subjects that qualified for the meta-analysis by Dinh *et al.* [25], the pooled sensitivity was 80%, but the specificity was only 28% [26,36,38,52,66,67]. The pooled diagnostic odds ratio was 2.1, indicating poor discriminating ability, while the *Q* statistic was 0.6, indicating moderate accuracy for the diagnosis of osteomyelitis [25]. On the basis of seven studies, Kapoor *et al.* [55] found the performance characteristics of a triple-phase bone scan were markedly inferior to MRI [38,41,45,49,58,63,64], with a diagnostic odds ratio of 3.5 (CI 1.0–13) *versus* 150 (CI 55–411), respectively [55]. Healthy bone may also have an increased uptake of the radiopharmaceutical, especially in the forefoot [65]. While a positive bone scan is certainly not specific for osteomyelitis (or CN), a negative one largely rules it out.

Radiolabelled white blood cells (usually using either ^{99m}Technetium or ^{111}Indium) are generally not taken up by healthy bone, making positive leukocyte scans more specific than bone scans for diagnosing osteomyelitis (and excluding CN) [65]. In a review of these scans by Capriotti *et al.*, the summary positive predictive values for osteomyelitis were 90% and 72%, respectively, and the negative predictive values were 81% and 83%, respectively [65]. ^{99m}Tc labelling appears to provide superior physical characteristics, leading to better spatial resolution than ^{111}In [65]. In another recent review, Palestro and Love concluded that among radionuclide procedures, labelled leukocyte imaging is the best choice for evaluating diabetic pedal osteomyelitis, with a sensitivity of 72% to 100% and specificity of 67% to 98% [68]. Dinh *et al.* [25] identified six studies using ^{111}Indium-radiolabelled leukocytes, with a pooled sensitivity of 74% and a specificity of 68% [26,36,38,52,66,67]. The pooled diagnostic odds ratio was 10, indicating moderately good discriminating characteristics, while the *Q* statistic of 0.59 suggests a low to moderate accuracy for the diagnosis of osteomyelitis [25]. Kapoor *et al.* [55] found that in three studies, MRI outperformed leukocyte scanning (with ^{99m}Tc [64] or ^{111}In [45,49]) with diagnostic odds ratios of 120 (CI 62–234) and 3.4 (CI 0.2–62), respectively. The combination of labelled leukocytes with a bone scan (dual tracer technique) does not substantially improve diagnostic accuracy [46].

Other available nuclear medicine techniques include *in vivo* methods of labelling leukocytes, radiolabeled polyclonal IgG and radiolabelled 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 immunoglobin G uptake is related to vascular permeability, not inflamed tissue, and thus not as specific as radiolabelled leukocytes [50,69]. The pooled positive and negative predictive values for this technique, calculated from 97 lesions, were 72% and 88%, respectively [65].

Other imaging techniques. Two published studies of computer tomography (CT) and CT combined with positron

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emission tomography (PET) scans for the diagnosis of osteomyelitis [25] did not include histopathological examination of bone [70,71]. A recent prospective study that enrolled 110 patients reported that PET/CT scan had a sensitivity of 81%, specificity of 93%, positive predictive value of 78%, negative predictive value 94% and accuracy of 90%, which was somewhat better than a simultaneous MRI [72]. While the data on this new procedure are limited, there seems to be a place for CT (especially if combined with PET) scans when MRI is unavailable or contraindicated.

Bone biopsy

The weight of current 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 profile [3]. Soft tissue or sinus tract cultures are not sufficiently accurate in predicting bone pathogens [73,74]. Ideally, it would be best to process a bone specimen for both culture and histopathology. While infected bone usually has inflammatory cells (granulocytes early and mononuclear cells later), the histomorphology of uninfected bone is normal in diabetic patients, including in those with neuropathy or vasculopathy [75]. Unfortunately, both histology and culture may be misleading results. Culture of a bone specimen may be falsely negative because of sampling errors, prior antibiotic therapy or a failure to isolate fastidious organisms. It may also be falsely positive because of contamination by wound-colonizing flora not involved in bone infection. Similarly, bone histopathology may be falsely negative due to sampling error or potentially falsely positive due to some non-infectious inflammatory disorder. In a recent analysis of 44 patients, a comparison of microbiological and histopathological testing demonstrated that they performed similarly in identifying the presence of pedal osteomyelitis in the diabetic foot [76].

In one retrospective multicentre study, using bone culture-guided antibiotic treatment was associated with a significantly better clinical outcome than using soft tissue culture results [77]; this finding requires confirmation by a prospective study. While success rates of 75% or higher have been reported with empiric treatment of diabetic foot osteomyelitis (DFO) it is difficult to compare the results of available published studies because of their differences in the populations enrolled, in the criteria for both diagnosis and remission of infection and in durations of follow-up [78]. 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 of non-informative data from soft tissue cultures, 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. rifampin, fluoroquinolones, fusidic acid or clindamycin) [2].

To reduce the likelihood of false-negative culture results, it is presumably best to perform bone biopsy after an antibiotic-free period in clinically stable patients. As certain antibiotic agents have a prolonged release from bone tissue, holding antibiotics for 2 weeks is ideal, but even a couple of days may be helpful [79]. Because DFO (in the absence of substantial soft tissue infection) is typically a slowly progressive disease, such a delay is usually safe. Percutaneous biopsy of bone through clinically uninvolved skin reduces the likelihood of false positive culture, although one study found good results (based on favourable clinical outcome) using a simpler per-wound bone biopsy after careful debridement [79]. Similarly, while there are potential risks of bone biopsy, that is, tracking contaminating organisms into the bone or causing a bone fracture, several large series have shown that complications from percutaneous (and surgical) procedures are very rare [26,80]. Any properly trained physician (e.g. a foot surgeon, interventional radiologist) can perform the biopsy. Percutaneous biopsy should preferably be performed under fluoroscopic or CT guidance, traversing intact and uninfected skin. Patients with sensory neuropathy often do not need anaesthesia. If possible, the operator should attempt to obtain at least two specimens – one for culture and the other for histological analysis. With small toe bones, it may only be possible to aspirate a few bony spicules.

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

Assessing severity

Accurately assessing a diabetic foot wound usually requires debridement of callus and necrotic tissue. Keys to classifying a foot infection are defining the extent of the tissues involved, determining the adequacy of arterial perfusion and assessing for systemic toxicity [16,82,83]. While mild infections are relatively easily treated, moderate infections may be limb threatening and severe infections may be life threatening (Table 3A). Infection severity largely guides the choice of antibiotic and its route of administration and helps to determine the need for hospitalisation (Table 3B), the potential necessity and timing of foot surgery and the likelihood of amputation [15,83–85].

Deep space infections may have deceptively few superficial signs, but clinicians should consider this possibility in a patient with systemic toxicity (e.g. fever, chills, leukocytosis), inflammation distant from the skin wound, persistent infection or elevated inflammatory markers despite appropriate therapy, or pain in a previously insensate foot [13,22,86].

Microbiological considerations

When to send specimens for culture

Knowing the likely etiologic agent(s) helps the clinician select appropriate antimicrobial therapy. Acute infections in previously untreated patients are usually caused by

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Table 3. 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 into subcutaneous tissues, i.e., fascia, tendon, muscle, joint, bone
Cellulitis	Extensive (>2 cm), distant from ulceration or rapidly progressive
Local signs	Severe inflammation, crepitus, bullae, marked induration, discoloration, necrosis/gangrene, ecchymoses or petechiae
General	
Presentation	Acute onset or rapidly progressive
Systemic signs	Fever, chills, hypotension, confusion, volume depletion
Laboratory tests	Leukocytosis, severe or worsening hyperglycaemia, acidosis, azotaemia, electrolyte abnormalities
Complicating features	Presence of a foreign body (accidental or surgically implanted), puncture wound, abscess, arterial or venous insufficiency, lymphoedema
Current treatment	Progression while on apparently appropriate antibiotic therapy
(B) Factors suggesting hospitalization may be necessary	
•Severe infection (Table 3A)	
•Metabolic instability	
•Intravenous therapy needed (and not available/appropriate as outpatient)	
•Diagnostic tests needed that are not available as outpatient	
•Critical foot ischemia present	
•Surgical procedures (more than minor) required	
•Failure of outpatient management	
•Patient's inability or unwillingness to comply with outpatient-based treatment	
•Need for more complex dressing changes than patient/caregivers can provide	

aerobic gram-positive cocci (often as a monomicrobial infection) [87], but deep or chronic wounds may harbour polymicrobial flora, including gram-negative and anaerobic bacteria [82]. Skin disorders, environmental exposures or recent antibiotic therapy can predispose to unusual or antibiotic-resistant pathogens. Wound cultures are helpful for most infections but are difficult to obtain in cases with just cellulitis (where skin aspiration has limited sensitivity) and generally unnecessary for clinically uninfected lesions. Blood cultures are only needed for severe infections, and bone cultures help diagnose and direct therapy of osteomyelitis. In the past decade, molecular microbiological techniques have demonstrated a far more complex mix of organisms in DFIs [88,89], but the clinical significance of these isolates is not yet clear.

Obtaining specimens for wound cultures

A wound culture is useful only if the specimen is appropriately collected and processed. Antibiotic susceptibility results generally help in focusing (and often constraining) antibiotic regimens. Deep tissue specimens, obtained aseptically at surgery, usually contain only the true pathogens, while cultures of superficial lesions often yield contaminants [87,90]. Curettage (tissue scraping) with a curette or scalpel from the base of a debrided ulcer or needle aspirate of purulent secretions generally provides more accurate results than wound swabbing [87,91]. If swabs are the only available method, they should be taken only after debriding and cleaning the wound. Specimens should be sent to the laboratory promptly, in suitable sterile transport containers.

Interpreting wound culture results

Sole or predominant bacteria identified on culture (and, where available, Gram-stained smear) and isolated from reliable specimens are likely true pathogens. If multiple organisms are isolated, especially from superficial ulcers, it can be difficult to determine which are pathogens. Targeting treatment against less virulent isolates (e.g. coagulase-negative staphylococci, corynebacteria) may be unnecessary. These species can, however, represent true pathogens, especially if they grow repeatedly or from reliable specimens. *Staphylococcus aureus* is the most frequently isolated and among the more virulent pathogens in DFIs; even when it is not the sole isolate, it is usually a component of a mixed infection. 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 hospitalisation are often polymicrobial, including aerobes and anaerobes [16,92]. Gram-negative bacilli (mainly Enterobacteriaceae, sometimes *Pseudomonas aeruginosa* or other non-fermentative 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 are the most frequent isolates in DFIs occurring in patients in warm climates, especially in developing countries [93–96]. It is unclear if this is related to environmental factors, footwear preferences, personal hygiene practices, antimicrobial pretreatment or other factors. Obligate anaerobic species are most frequent in wounds with ischaemic necrosis or those that involve deep tissues; they are rarely the sole pathogen and most often are part of a mixed infection with aerobes [97].

Multidrug-resistant organisms, especially methicillin-resistant *S. aureus* (MRSA), are more frequently isolated from patients who have recently received antibiotic therapy, have been previously hospitalized or reside in a chronic care facility [98]. After the rates of MRSA dramatically increased in many countries starting in the late

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1990s, they have begun to decline in most recent reports, concomitant with improved hospital (and outpatient) infection control measures [99–101]. The previously useful distinction of community-acquired (less likely to be resistant to other antibiotics) *versus* healthcare-associated strains has become blurred in recent years. In some, but not all, reports on DFIs, those caused by MRSA have been associated with worse outcomes, that is, higher clinical failure and amputation rates [102–104]. In the past decade, other multidrug-resistant organisms, especially gram-negatives with extended-spectrum beta-lactamases (ESBL) and occasionally vancomycin-resistant enterococci, have been more commonly isolated from DFIs [96,105,106]. ESBL-producing organisms usually require treatment with very broad-spectrum antibiotics, that is, carbapenems. Fungi may be isolated from both infected and uninfected foot wounds, but this rarely necessitates systemic antifungal therapy [107]. They are, however, a frequent cause of onychomycosis.

Bone infection

DFO can present the clinician with formidable diagnostic and therapeutic challenges [78]. It complicates about 50% to 60% of serious, and 10% to 20% of apparently less severe, foot infections in patients presenting to diabetic foot clinics. Bone infection typically occurs by contiguous spread from overlying soft tissue, which may penetrate through the cortex into the marrow. Bone destruction caused by neuroarthropathy (CN) may be difficult to distinguish from that caused by infection, although the former is less common, tends to occur in patients with profound peripheral neuropathy but adequate arterial perfusion, more frequently involves the midfoot and often occurs in the absence of a skin break [108,109]. Many cases of osteomyelitis are monomicrobial, but most are polymicrobial; *S. aureus* is the most commonly isolated agent (~50% of cases), while *S. epidermidis* (~25%), streptococci (~30%) and Enterobacteriaceae (~40%) are also frequent isolates [108].

Treatment

Patients with a severe infection (Table 3A) should usually be hospitalised, as they often require surgical interventions, fluid resuscitation and control of metabolic derangements. Also, consider admitting patients with moderate infections if they are unable or unwilling to be adequately involved in wound care, can or will not be able to off-load the affected area, are unlikely to comply with antibiotic therapy, require parenteral antibiotic therapy (that is not available as an outpatient) or need close monitoring of treatment response (Table 3B). Most other patients with a moderate infection, and almost all with a mild infection, can cautiously be treated as outpatients, with instructions to return if the infection worsens or in-office re-evaluation every few days initially [91].

Surgery is the cornerstone of treating many deep soft tissue infections [86], and early intervention might be associated with better outcomes [22,110–112]. Intervening emergently, however, is only needed in specific circumstances, such as severe infection in an ischaemic limb; an abscess accompanied by compartment syndrome or necrosis; systemic sepsis syndrome; or local infection with bullae, ecchymoses, extreme pain or unexpected anaesthesia. The treating clinician should consider the need for surgery in every infection, which may range from minor debridement or drainage to extensive resections 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. Major amputation should, and usually can, be avoided except when the limb is non-viable, is affected by life-threatening infection (e.g. gas gangrene or necrotizing fasciitis) or is functionally useless. Revascularisation may be needed for an infected ischemic limb. Surgeons operating on a patient with a DFI should have adequate knowledge of the complex anatomy of the foot [22,113]. Figure 1 shows an algorithmic overview of the approach to treating a diabetic patient with a foot lesion.

Antimicrobial therapy

Indications for therapy

Infected diabetic foot wounds require antibiotic therapy, as failure to properly treat infected wounds is usually associated with progressive tissue destruction and poor wound healing. Because antibiotic therapy is associated with frequent adverse effects, financial costs and increasing risk of antibiotic resistance [98], it should be reserved for treating wounds that are infected. Using antimicrobial therapy has not been proven beneficial for managing clinically uninfected skin wounds, irrespective of theoretical considerations of the bacterial 'bioburden' of chronic wounds [114–118]. There is no published evidence that they either accelerate wound healing or reduce 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 either as uninfected or as infected (using an infection grading system) and then carefully monitor progress.

Route of therapy

For an antibiotic to reach a therapeutic concentration at the site of infection, it must first achieve an adequate serum level [119]. Because parenteral antibiotics achieve faster and higher serum levels, they are recommended for patients who are systemically ill or have a severe infection. They may also be required for those unable to tolerate oral agents or who are infected with pathogens insensitive to oral agents. After the patient's clinical condition has stabilized and the infection is responding, most can switch to oral therapy. Where available, outpatient intravenous therapy can be used for those requiring prolonged parenteral treatment, for example for some cases of osteomyelitis or infections resistant to oral agents.

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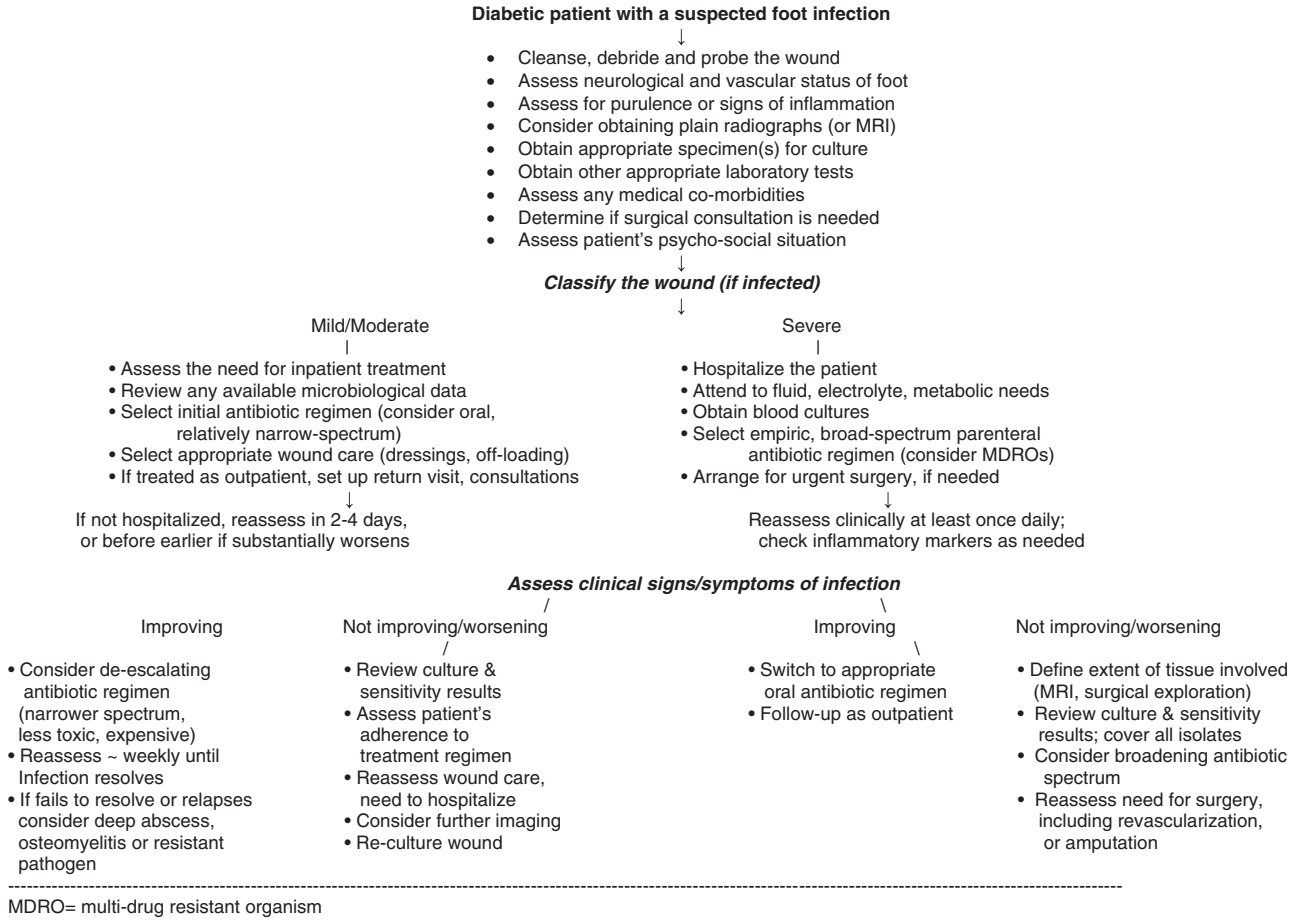

Figure 1. Approach to the infected diabetic foot

Compared with parenteral therapy, oral antibiotics are more convenient, generally associated with fewer complications and are less expensive. Gastrointestinal absorption of oral antibiotics, while variable, is excellent for several agents. Fluoroquinolones in particular achieve high tissue concentrations in DFIs [119–121], even in patients with gastroparesis [122], but most other currently used oral antibiotics also achieve adequate serum and tissue levels. 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) and good oral bioavailability. They are, however, generally considerably more expensive and have a shorter track record for safety evaluations.

Peripheral vascular disease, but not diabetes alone, may limit the delivery, and therefore penetration, of antibiotics to infected foot tissues [122,123]. Even in an ischemic limb, however, antibiotics play an important role in 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 [124,125], intra-arterial (e.g. femoral) administration [126] or primary closure of debrided wounds with catheter instillation of antibiotics [127]. These techniques have not yet proven their usefulness.

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 [128]. It also allows treatment with agents not available for systemic therapy. While not appropriate when there is extensive (>2 cm) cellulitis, a large randomized trial found an investigational topical antibiotic peptide (pexiganan) as effective as oral therapy with a fluoroquinolone for mildly infected diabetic foot ulcers [129]. 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 treating, mild infections [115]. Available data are too limited to recommend local antimicrobial treatment, but further research is warranted [130–132]. For deep wounds, antibiotic-loaded beads, cement or biodegradable bovine collagen sponges can supply high local antibiotic concentrations for a long duration and, in some instances, fill dead space [133,134]. A recent systematic review concluded that the data supporting the use of gentamicin-loaded beads is too limited to allow making recommendations [135].

Choice of antibiotics

Initial antibiotic regimens are usually empirical. These should cover the most common pathogens but be modified according to infection severity and available clinical

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or microbiological clues. Relatively narrow-spectrum agents are preferred for minor infections, with adjustments if clinical response is inadequate. Initial regimens for severe infections should be a broader spectrum, and treatment must be delivered promptly. An empirical regimen must also take into consideration factors related to the current infection, the likely pathogen(s), the specific patient and potential drug-related issues (Table 4). 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 [136].

An empiric regimen should virtually always include an antibiotic active against non-resistant isolates of staphylococci and streptococci. Consider adding an agent active against MRSA if the patient has risk factors for this organism (e.g. recent stay in healthcare setting, 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 for *Enterococcus* species. Empiric anti-anaerobic therapy is appropriate for necrotic, gangrenous or foul-smelling wounds. 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. rifamp(ic)in) to which resistance may quickly develop when used alone.

When culture and sensitivity results are available, consider changing to a more specific regimen targeted at 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 [137]. If the infection is not responding, however, modify treatment to cover all isolated organisms. If the infection is worsening despite the isolated bacteria being susceptible to the selected regimen, reconsider whether surgical intervention is needed, the possibility that fastidious infecting organisms were not recovered on culture or that patient adherence to the treatment regimen has been suboptimal.

Table 4. 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)
– History of colonisation or infection with MDROs
– Local rates of antibiotic resistance
Patient related
– Allergies to antibiotics
– Impaired immunological status
– Patient treatment preferences
– Renal or hepatic insufficiency
– Impaired gastrointestinal absorption
– Arterial insufficiency in affected limb
– Exposure to environment with high risk of MDROs or unusual pathogens
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 *C. difficile* disease or antibiotic resistance
– Published efficacy data

GPC, gram-positive cocci (aerobic); MDRO, multidrug-resistant organism.

Several antibiotic agents have been used successfully to treat DFIs for decades, despite not having been evaluated in prospective comparative studies; these include penicillinase-resistant penicillins (e.g. dicloxacillin, nafcillin), cephalosporins (e.g. cefazolin, ceftriaxone), glycopeptides (teicoplanin), rifampi(ci)n, fusidic acid, pristinamycin, trimethoprim–sulfamethoxazole and doxycycline. Agents that have demonstrated clinical effectiveness, alone or in combination, in published prospective studies of DFIs include the following (Table 5) [3]:

- Cephalosporins (cephalexin orally; cefoxitin and ceftizoxime, parenterally)
- Penicillin/β-lactamase inhibitor congeners (amoxicillin/clavulanate, orally; ampicillin/sulbactam, piperacillin/tazobactam and ticarcillin/clavulanate, parenterally)
- Carbapenems (imipenem/cilastatin and ertapenem, parenterally)
- Fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin and moxifloxacin, all both orally and parenterally)
- Other agents: clindamycin (orally and parenterally); amdinocillin (parenterally); linezolid (orally and parenterally); daptomycin (parenterally); and vancomycin (parenterally)

Other agents in the same antibiotic classes as those listed (or in Table 5) 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 [2,3,103,138,139]. 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 [136,138]. 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 [140]. There is a compelling need for comparative trials and economic analyses of various anti-infective regimens for DFIs [141,142]. Suggested empirical antibiotic regimens, by type of infection, are given in Table 5.

Duration of therapy

The optimal duration of antibiotic therapy for various types of DFIs is unknown. On the basis of data from available studies, for mild to moderate infections, 1 to 2 weeks

Table 5. Selecting an empiric antibiotic regimen for diabetic foot infections

Infection severity	Additional factors	Usual pathogen(s)	Potential empirical regimens[1]
Mild			
	No complicating features	GPC (staphylococci or streptococci)	S-S pen; first gen Ceph[2]
	Recent antibiotic exposure	GPC + GNR	β-L-ase-1; T/S; FQ
	Beta-lactam allergy or intolerance		Clindamycin; FQ; T/S; macrolide
	High risk for MRSA	MRSA	Linezolid; T/S; doxycycline
Moderate and severe[3]			
	No complicating features	GPC ± GNR	β-L-ase 1; second/third gen Ceph
	Recent antibiotics		β-L-ase 2; second/third gen Ceph, group 1 carbapenem (depends on prior therapy; seek advice)
	Macerated ulcer, warm climate	GNR, including *Pseudomonas*	FQ; β-L-ase 2; group 2 carbapenem
	Ischemic limb/necrosis/gas forming	GPC ± GNR ± anaerobes	β-L-ase 1 or 2; group 1 or 2 carbapenem; or second/third gen Ceph + clindamycin or metronidazole
	MRSA risk factors	MRSA	Consider addition of, or substituting with, glycopeptides, linezolid, daptomycin; fusidic acid, T/S, doxycycline
	Risk factors for resistant GNR	*Pseudomonas**/ESBL	Pip/tazo*, carbapenems, FQ, aminoglycoside, colistin

β-L-ase = β-lactam, β-lactamase inhibitor.
β-L-ase 1 = amoxicillin/clavulanate, ampicillin/sulbactam.
β-L-ase 2 = ticarcillin/clavulanate, piperacillin/tazobactam.
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).
T/S = trimethoprim/sulfamethoxazole.
ESBL, extended-spectrum beta-lactamase; GPC, gram-positive cocci (aerobic); GNR, gram-negative rods; MRSA, methicillin-resistant *Staphylococcus aureus*.
[1]Given at usual recommended doses for serious infections. Modify doses or agents selected for azotaemia, liver dysfunction *etc*. Recommendations based upon theoretical considerations and available clinical trials.
[2]A high local prevalence of methicillin resistance among staphylococci may require using vancomycin or other appropriate anti-staphylococcal agents active against these organisms.
[3]Oral antibiotic agents should generally not be used for severe infections, except as follow-on (switch) after initial parenteral therapy.

is usually effective [3,91], while for more serious infections, 2 to 4 weeks is usually sufficient [3,137,143–145]. Antibiotic therapy can generally be discontinued when signs and symptoms of infection have resolved, even if the wound has not healed – antibiotics are employed to cure infection, not 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 justify and document the treatment strategy. 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

For DFIs, antibiotics are necessary but not sufficient to overcome inadequate vascular supply, poor glycaemic control or improper wound care [146,147]. Most wounds need to be carefully cleaned and debrided of necrotic tissue and surrounding callus. Those with heavy exudate need a dressing that absorbs the moisture, while dry wounds heal best in a moist environment. Dressings should optimally be changed at least daily, to allow careful examination of the wound. Published studies do not adequately support using any available topical antimicrobials on most wounds. For patients with a DFI, it is best not to use a device (e.g. a total contact cast, topical negative pressure) that does not allow easy daily visualization of the wound. Remove or redistribute any pressure from the wound by encouraging the patient to be non-ambulatory or by providing an appropriate off-loading device.

Treating osteomyelitis

The IWGDF has produced a full systematic review of, and guidelines for, the treatment of DFO [2]. Among the important factors to consider when treating osteomyelitis are the following: the anatomic site of infection, the local vascular supply, the extent of soft tissue and bone destruction, the presence of systemic signs of infection and the patient's preferences. 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 and no surgical intervention in about two-thirds of cases [77,148–150]. In these reports, clinicians have generally employed antibiotic doses at the higher recommended ranges and given for at least two (and usually 3–6) months. Unfortunately, available studies do not provide information to inform which cases may require surgery [77,148–150]. In some cases, limited surgery combined with antibiotic therapy may be most appropriate [112].

The choice of an antimicrobial agent for osteomyelitis should optimally be based on the results of a bone culture, especially because of the need for long-duration therapy [77,108]. If empiric therapy is necessary, always select a regimen that covers *S. aureus*, as it is the most common pathogen; the patient's history or culture results may suggest a need for broader coverage. Some antibiotics may not penetrate well to 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 antibiotics and improved outcome has not yet been studied. Traditionally, treatment of osteomyelitis has usually been parenteral (at least initially) and prolonged (at least 4 weeks), but these recommendations are not based on strong data. Many patients can probably be switched to oral therapy after about a week of parenteral treatment. Any oral antibiotics selected should have good bioavailability [e.g. fluoroquinolones, rifampi(ci)n (always combined with another agent), clindamycin 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 [3]. Extending post-debridement antibiotic therapy beyond six weeks, or giving IV treatment longer than one week, does not appear to increase the remission rate [151]. 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. Antibiotic impregnated beads [133] or orthopaedic implants have been used successfully to treat DFO in a few small series [134].

Adjunctive therapies

Several studies have reported the results of additional measures used in an effort to improve infection resolution, wound healing or host response. These include negative pressure wound therapy, recombinant granulocyte colony stimulating factor (G-CSF), systemic hyperbaric oxygen (HBO) and larval (maggot) therapy. The available evidence does not support that any of these should be routinely used specifically for treatment of infection. There may, however, be a role for some or all in the overall care of the patient with a diabetic foot wound, though the evidence for cost effectiveness remains weak. On the basis of the results of a meta-analysis of generally low-quality studies, G-CSF therapy is associated with significantly fewer surgical procedures, including amputations and duration of hospital stay, but not with the likelihood of resolution of infection, wound healing or the duration of systemic antibiotic therapy [3,152]. For HBO therapy, systematic reviews of largely poor quality randomised controlled trials (RCTs) [153], and a more recent well-done RCT [154], suggest a potential role in wound healing but have provided no evidence for a role in treating soft tissue or bone infection. For treating onychomycosis, there are many suggested remedies, including topical and oral medications and device-related methods. While oral antifungal therapy (e.g. itraconazole, terbinafine) is perhaps the best current treatment, newer methods (e.g. improved nail penetrating topical compounds, light based devices) appear to be promising [155].

Outcome of treatment

With appropriate treatment, the signs and symptoms of mild infections 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% [3,156]. 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 [157]. The presence of limb or foot ischemia has an important adverse effect on the outcome, synergising with infection to worsen the prognosis [158].

Unfortunately, having had one foot infection is associated with an increased likelihood of another; foot infection recurs in 20% to 30% of diabetic patients, especially those with underlying osteomyelitis [159]. While it is difficult to know when osteomyelitis is cured, evidence suggesting remission includes a drop in the erythrocyte sedimentation rate or C-reactive protein level, reconstitution of destroyed bone on plain radiograph and healing of any overlying soft tissue wound. 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, a peripheral white blood cell count of $<12\,000/mm^3$ and a lower extremity transcutaneous oxygen tension of >40 mmHg [9,160]. Because of the risk of reinfection, educating patients who have a DFI on prevention techniques and encouraging prompt consultation for foot problems are critical. While much has been learned about diagnosing and treating infections in the past few decades, many fundamental questions remain, and more research is required.

Issues of particular importance in developing countries

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, compared with more developed, countries. To begin with, in developing countries, infections are often a consequence of wounds caused by the diabetic person either wearing footwear that is not sufficiently protective (e.g. sandals) or poorly fitting, or wearing none at all. Moreover, the person may delay seeing a healthcare provider for a longer period of time because of a lack of financial resources, nearby clinics or proper education. During this period, the patient may attempt to treat the infection with various home remedies, including plants or other locally accepted treatments. Patients can often buy antibiotics without a prescription in developing countries; thus, they will often have treated themselves, sometimes with the advice of a pharmacist or other trusted but non-licensed persons, before presenting to a physician. This unsupervised treatment, sometimes with expired medications at inadequate doses, is likely to result in infections caused by more antibiotic-resistant organisms.

Healthcare providers in developing countries may also face added difficulties. They may not have access to a microbiology laboratory, so they cannot ascertain the identity and antibiotic susceptibility of foot pathogens infecting an individual patient or of current isolates in the community. Similarly, many will not have access to even basic (not to mention more sophisticated) imaging equipment. Even when a patient sees a physician and receives an antibiotic prescription, indigent patients may be unable to purchase the full course of therapy or may be prescribed inexpensive but potentially more toxic or less effective agents. Home or work circumstances may make it very difficult for them to stay off their foot, or to afford or be able to 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. 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).

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