Characteristic features of osteomyelitis on plain X-rays of the foot (usually 2 or 3 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]7, nine were prospective in design [26,36,38- 41,44,45,52]. Overall, the 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 [24], analyzing 7 studies of plain radiographs the summary positive likelihood ratio was 2.3 (95% confidence intervals 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 far more likely to predict the presence of osteomyelitis than a single study, although correctly targeted antibiotic therapy may prevent these changes.

B. Magnetic resonance imaging

MRI is a valuable tool for diagnosing osteomyelitis, as well as helping define 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 and coworkers [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] Only one study, however, 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 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 enrollment 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 to older ones, perhaps because their study designs were better. The subgroups of patients with other diagnoses (e.g., Charcot arthropathy) were too small to analyze any differences among the studies.

C. Nuclear medicine

Three recent meta-analyses reviewed nuclear medicine techniques for evaluating the diabetic foot [25,55,65]. Capriotti and coworkers reviewed 57 papers, including 7 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 99mTc-methylene diphosphate and done in timesequence 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 and coworkers [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]. Based on seven studies, Kapoor et al. [55] found the performance characteristics of to a triple-phase bone scan were markedly inferior to MRI [38,41,45,49,58,63,64], with a diagnostic odds ratio 3.5 of (CI 1.0-13) compared to 150 (CI 55-411) [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 Charcot neuro-osteoarthropathy), a negative one largely rules it out.

Radiolabelled white blood cells (usually using either 99mTechnetium or 111Indium) are generally not taken up by healthy bone, making positive leukocyte scans more specific than bone scans for diagnosing osteomyelitis (and excluding Charcot osteoarthropathy) [65]. In a review of these scans by Capriotti et al, the summary positive predictive values for osteomyelitis were 90% and 72%, respectively, the negative predictive values were 81% and 83%, respectively[65]. 99mTc labeling appears to provide superior physical characteristics, leading to better spatial resolution than 111In [65]. In another recent review, Palestro and Love concluded that among radionuclide procedures, labeled 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 and coworkers [25] identified 6 studies using 111Indium radiolabel 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 99mTc [64] or 111In [45,49]) with diagnostic odds ratios of 120 (CI 62-234) and 3.4 (CI 0.2-62), respectively. The combination of labeled 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 labeling leukocytes, radiolabeled polyclonal IgG, and radiolabeled antibiotics. Results of studies using these techniques have varied and most of the methods are unavailable in many countries. 99mTc-/111In labeled human immunoglobin G uptake is related to vascular permeability, not inflamed tissue, and thus not as specific as radiolabeled leukocytes [50,69]. The pooled positive and negative predictive values for this technique, calculated from 97 lesions were 72 and 88%, respectively [65].

D. Other imaging techniques

Two published studies of computer tomography (CT) and CT combined with positron 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%, somewhat better than a simultaneous MRI [72]. While the data on this new procedure are limited, there seems to be place for CT (especially if combined with PET) scans when MRI is unavailable or contraindicated.

5. Bone biopsy:

The weight of current evidence supports bone biopsy 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 accurately 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 lead to 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 multicenter study, using bone culture-guided antibiotic treatment was associated with a significantly better clinical outcome than using soft tissue culture results [77]. 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 their differences in the populations, in the criteria for both diagnosis and remission of infection they used, and in their durations of followup [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 an initial empiric antibiotic therapy, or when considering an antibiotic regimen with a high 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 two-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, e.g., 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., an orthopedic surgeon, podiatrist or interventional radiologist) can perform the biopsy. Percutaneous biopsy should preferably be done 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 2 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.

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
- Sequestration: 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 (MRI)

- Low focal signal intensity on T-1 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

○ Adjacent soft tissue inflammation or edema
For both modalities, bony changes are often accompanied by contiguous soft tissue swelling

V. 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 hospitalization (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 these 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].

Table 3

Characteristic 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, e.g. 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 or rapidly progressive
Systemic signs	Fever, chills, hypotension, confusion, volume depletion
Laboratory tests	Leukocytosis, severe or worsening hyperglycemia, acidosis, azotemia, electrolyte abnormalities
Complicating features	Presence of a foreign body (accidental or surgically implanted), puncture wound, abscess, arterial or venous insufficiency, lymphedema
Current treatment	Progression while on apparently appropriate antibiotic therapy
(B) Factors suggesting hospitalization may be necessary	
• Severe infection (see Table 3A) • Metabolic instability • Intravenous therapy needed (and not available/appropriate as outpatient) • Diagnostic tests needed (and not available as outpatient)	

- Critical foot ischemia present
- Surgical procedures (more than minor) required
- Failure of outpatient management
- Inability or unwillingness to comply with outpatient-based treatment
- Need for more complex dressing changes than patient/carers can provide

VI. Microbiological considerations

A. 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 aerobic gram-positive cocci (often as a monomicrobial infection)[87], but deep or chronic wounds may harbor 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 (see above). In the past decade molecular microbiological techniques have demonstrated a far more complex mix of organisms in diabetic foot infections [88,89], but the clinical significance of these isolates is not yet clear.

B. 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 scalpel from the base of a debrided ulcer or needle aspirates of purulent secretions generally provide more accurate results than wound swabbing [87,91]. Where 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.

C. 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 less virulent isolates (e.g., coagulasenegative 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 virulent pathogen in diabetic foot infections; even when it is not the sole isolate, it is usually a component of a mixed infection. Streptococci (various groups of β-hemolytic, and others) are also important pathogens. Enterococci are relatively frequent isolates, but usually of secondary clinical importance.

Infections requiring hospitalization 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 practices, personal hygiene habits, antimicrobial pretreatment, or other factors. Obligate anaerobic species are most frequent in wounds with ischemic 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].

Multi-drug resistant organisms (MDROs), 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 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 (more-resistant) 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, e.g., 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 vancomycinresistant enterococci, have been more commonly isolated from DFIs [96,105,106]. ESBL-producing organisms usually require treatment with very broad-spectrum antibiotics, e.g., carbapenems. Fungi may be isolated from both infected and uninfec- ted foot wounds, but rarely require systemic antifungal therapy [107]. They are, however, a frequent cause of onychomycosis.

D. 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 (Charcot foot) 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].

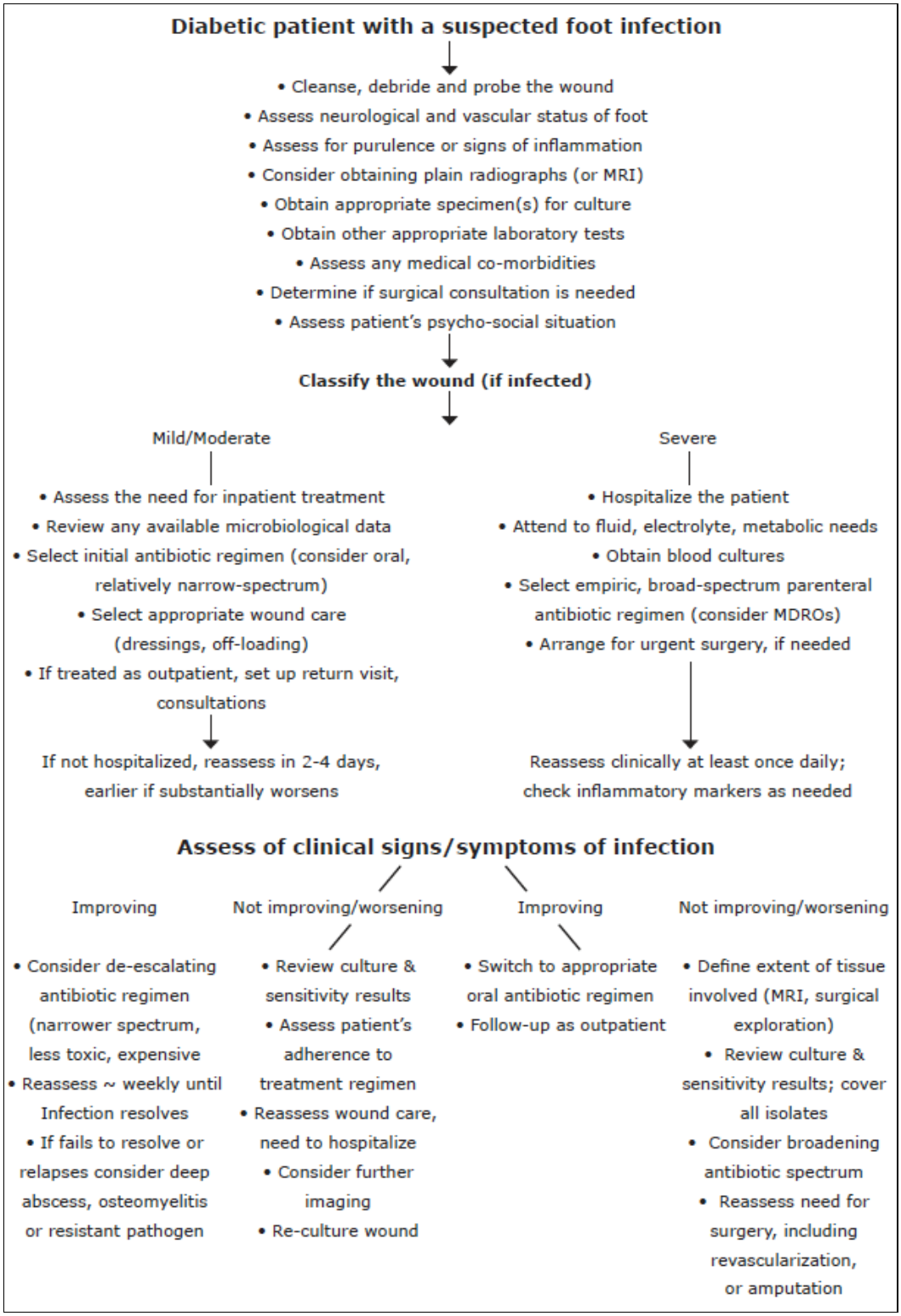
VII. Treatment

Patients with a severe infection (Table 3A) should usually be hospitalized, 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 (see 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 reevaluation 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 ischemic limb; an abscess accompanied by compartment syndrome or necrosis; systemic sepsis syndrome; or, local infection with bullae, ecchymoses, extreme pain, or unexpected anesthesia. 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. Revascularization 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.

Figure 1

Approach to a diabetic patient with a potentially infected foot wound Open in new window



MDRO= multi-drug resistant organism

A. Antimicrobial therapy

1. 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 as either uninfected or

as infected (using an infection grading system) and then carefully monitor progress.

2. 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 also 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.

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 diabetic foot infections [119-121], even in patients with gastroparesis [122], but most other currently used oral antibiotics 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 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 the dead space [133,134]. A recent systematic review concluded that the data supporting the use of gentamicin-loaded beads is too limited to allow recommendations [135].

3. 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 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 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 (see 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].

Table 4

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

Infection related
• Clinical severity of the infection (see Table 1) • History of antibiotic therapy within 3 months • Bone infection (presumed or proven) present
Pathogen related
• Likelihood of non-GPC etiologic agent(s) • History of colonization or infection with MDROs • ocal 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= multi-drug resistant organism

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 health-care 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., rifampin) 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 organisms were not recovered on culture, or that patient adherence to the treatment regimen has been suboptimal.

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 diabetic foot infections include the following (see 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)

Table 5

Infection Severity	Additional Factors	Usual Pathogen(s)	Potential Empirical Regimens[a]
Mild			
	No complicating features	GPC (staphylococci or streptococci)	S-S pen; 1st gen Ceph[b]
	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[c]			
	No complicating features	GPC ± GNR	β -L-ase 1; 2nd/ 3rd gen Ceph
	Recent antibiotics		β -L-ase 2; 2nd/ 3rd gen Ceph, group 1 carbapenem (depends on prior therapy; seek advice)
	Macerated ulcer, warm climate	GNR, including *Pseudomonas*	FQ; β -Lase-2; group 2 carbapenem
	Ischemic limb/ necrosis/ gas forming	GPC ± GNR ± anaerobes	β -L-ase 1 or 2; group 1 or 2 carbapenem; or 2nd /3rd 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/tazob actam
FQ = fluo roquinolone with good activity against aerobic gram-positive cocci (e.g., levofloxacin or moxifloxacin)
T/S = trimethoprim/sulfamethoxazole

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

[b] A high local prevalence of methicillin-resistance among staphylococci may require using vancomycin or other appropriate anti-staphylococcal agents active against these organisms.

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

Other agents in the same antibiotic classes as those listed 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 favor, 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.

4. Duration of therapy:

The optimal duration of antibiotic therapy for various types of diabetic foot infections is unknown.

Based on data from available studies, for mild to moderate infections, 1 to 2 weeks is usually effective [3,91,91], 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 aimed at curing infection, not healing wounds. More extended treatment may be needed for immunocompromised patients, for wounds that are poorly perfused, deep, large or necrotic wounds, 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.

B. Wound care

For DFIs antibiotics are necessary, but not sufficient to overcome inadequate vascular supply, poor glycemic 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 be changed at least daily, to allow careful examination of the wound. Available studies do not support using any 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 with an appropriate off-loading device.

C. Treating osteomyelitis

The IWGDF has produced a full systematic review of, and guidelines for, the treatment of diabetic foot osteomyelitis [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 diabetic foot osteomyelitis 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 diabetic foot osteomyelitis can be arrested (or even apparently cured) with antibiotic therapy alone 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 the 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 be 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 infections [133] or orthopedic implants have been used successfully to treat diabetic foot osteomyelitis in a few small series [134].

D. Adjunctive therapies

Several studies have reported the results of additional measures used in an effort to improve infection resolution, wound healing, and 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. Based on 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 RCTs [153], and one 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].

E. 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 favorable: many require surgical debridement, bone resection, or partial amputations. With extensive infection, or in medical centers with limited expertise or resources, lower extremity amputation rates of up to 50-60% have been reported [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 negative effect on the outcome, synergizing with infection to worsen the prognosis [158].

Unfortunately, having had a 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 mm/Hg or in the ankle of >80 mm/Hg, a peripheral white blood cell count of <12, 000/mm3, and a transcutaneous oxygen tension >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 is 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.

VIII. Issues of Particular Importance in Developing Countries

These guidelines must, of course, be adapted to the local circumstances in which a health care provider sees patients. Many aspects of the management of diabetic foot infections 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), 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 healthcare, 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 is likely to result in infections caused by more antibiotic-resistant organisms.

Physicians in developing countries may also face added difficulties. They may not have access to

a microbiology laboratory, so 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 (let alone 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 traveled a long distance to see a physician and cannot easily return for follow-up visits. Improving management of diabetic foot infections 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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