Microbiology and Treatment of Diabetic Foot Infections

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Abstract

Foot infections in diabetic patients are a major source of morbidity and an important proximate cause of amputations. These infections can be categorized clinically as limb threatening or non-limb threatening. The former are often caused by *Staphylococcus aureus* (often methicillin-resistant) and group B streptococci while the latter by these organisms and gram-negative bacilli and anaerobes. Multidrug-resistant pathogens are found in chronic infections, especially after exposure to health care and antibiotics. Effective treatment combines appropriate antimicrobial therapy with wound management and, if needed, surgical debridement. Osteomyelitis is common, often requiring surgical debridement for effective therapy. Although aspects of care could be refined by additional study, current evidence is sufficient to prevent or effectively treat most of these infections.

Keywords

Foot infection • Osteomyelitis • *Staphylococcus aureus* • Methicillin-resistant *S. aureus* • Multidrug-resistant bacteria • Infected ulcers • Amputations

The foot of patients with diabetes mellitus is affected by several processes which not only contribute to the development and progression of infection but on occasion alter the appearance of the foot in ways that may obscure the clinical features of local infection. Neuropathy involving the motor fibers supplying muscles of the foot causes asymmetric muscle strength, which in turn results in foot deformities and maldistribution of weight (or pressure) on the foot surface. Dysfunction of the sensory fibers supplying the skin and deeper structural elements of the foot allows minor and major injury to these tissues to proceed without appreciation by the patient. As a result of neuropathy, the foot may be dramatically deformed, ulcerate in areas of unperceived trauma (mal perforans), and on occasion be warm and hyperemic in response to deep structural injury (acute Charcot's disease). This warmth and hyperemia

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may be misinterpreted as cellulitis and an ulceration, while a major portal of entry for infection may be uninfected. In the patient with diabetes, peripheral neuropathy may develop in isolation or commonly in parallel with atherosclerotic peripheral vascular disease. The latter involves major in-flow vessels to the lower extremity but commonly is associated with occlusive lesions of the tibial and peroneal arteries between the knee and ankle. The resulting arterial insufficiency can alter the appearance of the foot and obscure infection. Rubor may reflect vascular insufficiency rather than inflammation and conversely pallor may mute the erythema of acute infection. Gangrene and necrosis may be primarily ischemic or may reflect accelerated ischemia in the setting of infection. In sum, the diagnosis of infection involving the foot in patients with diabetes requires a careful detailed examination of the lower extremity and its blood supply.

The Diagnosis of Foot Infections

The initial step in the diagnosis of a foot infection in a patient with diabetes is to recognize those patients at greatest risk and to suspect infection. Clinical factors that have been significantly associated with foot infection include peripheral vascular disease with absent arterial pulses or an ankle brachial index of <0.9, loss of protective sensation, a history of recurrent foot ulcers or prior amputation, foot ulcers of >30 days duration, a wound that extends to bone, i.e., a positive probe to bone test (see Sect. "Osteomyelitis"), and a traumatic wound [1, 2]. Thereafter, infection is diagnosed clinically and to varying degrees supported by test results. Finding purulent drainage (pus) or two or more signs or symptoms of inflammation (erythema, induration, swelling, pain, tenderness, or warmth) is indicative of infection. Clinical signs on occasion belie the significance and severity of infection. A minimally inflamed but deep ulceration may be associated with underlying osteomyelitis [3]. Serious limb-threatening infection may not result in systemic toxicity. For example, among patients hospitalized for limb-threatening infection only 12–35% have significant fever [4–6]. In fact, fever in excess of 102°F suggests infection involving deeper spaces in the foot with tissue necrosis and undrained pus, extensive cellulitis, or bacteremia with the potential for hematogenous seeding of remote sites. Laboratory studies may be supportive of the diagnosis of these infections but must be interpreted in the context of clinical findings. Thus, the erythrocyte sedimentation rate and C-reactive protein concentration may be normal in infected patients and in up to 50% of patients with deep foot infection the white blood cell count may be normal [7]. Elevated concentration of C-reactive protein and procalcitonin can help distinguish mild or moderately infected ulcers from those that are uninfected [8]. Open skin wounds and ulcerations are often contaminated or colonized by commensal organisms that on occasion become pathogens. As a consequence, cultures while essential in the assessment of the microbiology of foot infections, do not in isolation establish the presence of infection. Unless the cultured material is obtained from deep tissue planes by percutaneous aspiration, the results of cultures must be interpreted in the clinical context.

The Severity of Foot Infections

Multiple classification schema have been designed to define the severity of foot wounds with or without infection in patients with diabetes. Some such as the widely used Wagner system include infection only in one grade [9]. Others, focused on subtle grading of features of infection, require a scoring sheet and are thus too complex for routine clinical use. The Infectious Diseases Society of America (IDSA) classification utilizes depth of a wound, presence of ischemia, presence and extent of infection, and systemic toxicity to designate the severity of foot infection. This schema classifies wounds from having no infection to being severely infected (Table 18.1) [10]. Increased severity in the IDSA classification schema, e.g., moderate and severe infection, correlates with the need for hospitalization and amputation [11].

Table 18.1 Classification of severity of diabetic foot infection

Clinical manifestation of infection	Infection severity[a]
Wound lacking purulence of any manifestations of inflammation	Uninfected
Presence of ≥2 manifestations of inflammation (purulence, or erythema, pain, tenderness, warmth, or induration), but any cellulitis/erythema extends ≤ 2 cm around the ulcer, and infection is limited to the skin or superficial subcutaneous tissues; no other local complications or systemic illness	Mild
Infection (as above) in a patient who is systemically well and metabolically stable but which has ≥ 1 of the following characteristics: cellulitis extending > 2 cm, lymphangitic streaking, spread beneath the superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint or bone	Moderate
Infection (moderate) in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	Severe

Adapted from ref. [10] with permission
[a] In the setting of severe ischemia, all infections are considered severe

A simple practical classification of foot infection into limb-threatening or non-limb threatening has also been described [12]. In this schema, infection is categorized primarily based on depth of the tissues involved, this being largely function of depth of a predisposing ulceration, and the presence or absence of significant ischemia. Patients with non-limb-threatening infection have superficial infection involving the skin, lack major systemic toxicity, and do not have significant ischemia. What might have been a non-limb-threatening infection becomes limb threatening in the face of severe ischemia. In a non-limb-threatening infection, an ulceration does not penetrate fully through skin. Limb threatening infection, when not categorized as such based on severe ischemia, involves deeper tissue planes with the portal of entry being an ulcer which has penetrated at least into subcutaneous tissue or potentially deeper to tendon, joint, or bone. Although limb threatening infections may be dramatic with extensive tissue necrosis, purulent drainage, edema, and erythema, they may be cryptic as well. Thus, an infected deep ulcer with a rim of cellulitis that is ≥2 cm in width is considered limb-threatening. Of note, hyperglycemia occurs almost universally in patients with non-limb-threatening and limb-threatening infection. In contrast, significant fever occurs in only 12–35% of patients with limb-threatening infection [4–6]. Fever is found primarily in these patients with extensive cellulitis and lymphangitis, infection (abscesses) loculated in the deep spaces of the foot, bacteremia, or hematogenously seeded remote sites of infection.

Mild or less extensive moderate infection by the IDSA guidelines would be considered non-limb-threatening infection in this simplified schema. Infection categorized by the IDSA schema as more extensive moderate or severe would be judged limb-threatening infection in this simplified schema. The simple classification, when adjusted for prior medical therapy and antibiotic exposure which is likely to result in infection by resistant organisms, allows one to anticipate the organisms causing wound infections and thus is an excellent point of departure from which to plan empiric antimicrobial therapy.

Microbiology

Cultures of open foot ulcers cannot be used to establish the presence of infection. Foot ulcers whether infected or not will contain multiple commensal or colonizing bacteria, some of which have the potential to become invasive pathogens. As a foot ulcer transitions from uninfected to infected, organisms isolated from the ulcer cavity include both colonizing flora and invasive pathogens. Assigning specific significance to organisms isolated from ulcers may be difficult. Sapico and colleagues demonstrated that the organism cultured from specimens obtained by aspiration or by curettage of the base of a cleansed ulcer were most concordant with those isolated from necrotic infected tissue excised from adjacent to the ulcer

base [13]. Of note, cultures of aspirated material failed to yield pathogens recovered from curettage or excised tissue in 20% of patients. Although not endorsed strongly by the IDSA guidelines or other experts, culture of material obtained on swabs of the deep ulcer base may provide useful information. Slater, et al., found that in wounds that did not extend to bone essentially the same organisms were recovered from cultures of swab specimens and deep tissue specimens. When wounds extended to bone, swab cultures recovered only 65% of organisms cultured from deep tissues [14]. Pellizzer et al. also found that on initial wound cultures swab specimens taken from deep in the ulcer yielded the same bacterial species as did cultures of deep tissue biopsies, with the exception that *Corynebacterium* species, likely colonizers or contaminants, were isolated from swab cultures [15].

Although the microbiology from clinical reports, wherein most specimens are obtained through the ulceration, requires interpretation to adjust for the inclusion of organisms of known low invasive potential and likely to be commensals or colonizers, it is possible to sense the major pathogens causing non-limb-threatening and limb-threatening foot infections. When surgical or aspiration specimens are not readily available for culture, antibiotic therapy can be designed with reasonable confidence based upon the culture results from specimens obtained by curettage of the ulcer base. Accordingly, culture of material obtained from an ulcer base by curettage, after the ulcer has been cleansed and debrided is recommended. Culture of material swabbed from an ulcer base is a less desirable alternative. The exception to the utility of cultures obtained from ulcers is in the design of antimicrobial therapy for osteomyelitis when the infected bone is to be debrided piecemeal, as opposed to resected en bloc. In this situation, more precise biopsy based culture information is highly desirable [10, 16].

In non-limb-threatening infections, particularly those occurring in patients who have not previously received antimicrobial therapy, *Staphylococcus aureus* and streptococci, particularly group B streptococci, are the predominant pathogens [10, 16–20]. *S. aureus* has been isolated from more than 50% of these patients and in more than 30% *S. aureus* is the only bacterium isolated [17]. Recently, as in other skin and soft tissue infections, *S. aureus* causing infections in the feet of diabetics are increasingly methicillin-resistant (MRSA), the prevalence increasing from 11.6 to 21.9% from 2003 to 2007 in one study [21]. Other studies have also noted an increase in the percent of *S. aureus* that are methicillin-resistant [22–24].

Limb-threatening foot infections, which often involve deeper tissues and are typically chronic as well as previously treated, are generally polymicrobial. Cultures from these infections yield on average 2.3–5.8 bacterial species per culture. Both gram-positive cocci and gram-negative rods are commonly isolated from a single lesion and in 40% of infections both aerobic and anaerobic organisms are recovered [4, 10, 13, 16, 18, 20, 25–27] (Table 18.2). Individual cultures have yielded on average 2.9–3.5 aerobes and 1.2–2.6 anaerobes [28]. *S. aureus* (including methicillin-sensitive and methicillin-resistant isolates), streptococci (particularly group B streptococci), and facultative gram-negative bacilli (*Proteus* species, *Enterobacter* species, *Escherichia coli*, *Klebsiella* species) and *Pseudomonas aeruginosa* are the predominant pathogens in these infections. Among the anaerobes, *Peptostreptococcus* species, *Prevotella* species, and *Bacteroides* species, including those of the *B. fragilis* group, are recovered frequently [28, 29]. Of note, *Clostridium* species are recovered infrequently. Although anaerobes are recovered from 41 to 53% of limb-threatening infections in clinical trials, with optimal methods these organisms can be recovered from 74 to 95% of these infections [28]. The frequency of isolating anaerobic bacteria is greatest in those patients with the most severe infections, particularly those where infection involves necrotic gangrenous tissue and amputation is often required. Nevertheless, the clinical features of foot infections, beyond those which allow categorization as non-limb threatening or limb threatening, are not sufficiently sensitive clues to allow defining the specific microbiology of these infections. Fetid infections suggest infection

Table 18.2 Microbiology of limb-threatening infections in patients with diabetes[a]

Organisms	Percent of patients (number patients)						
	Gibbons et al. (42)	Hughes et al. (50)	Bamberger et al. (51)	Scher et al. (65)	Grayson et al. (96)	Citron et al. (427)	Gadepalli et al. (80)
Aerobic							
S. aureus	22	25	22	23	54	15	14
S. epidermidis	12	14	19	18	12	11	8
Enterococcus spp.	16	17			28	12	11
Streptococcus spp.	13	20	41	54	55	10	
Corynebacterium spp.	7		8			7	
E. coli	7	3	1	19	6	1	12
Klebsiella spp.	4	7	4	10	5	2	7
Proteus mirabilis	11	11	5	36	9	2	13
Enterobacter spp.	3	7	7		9	2	1
Other							
Enterobacteriaceae	2	5	7	50	17	2	10
P. aeruginosa	3	0	5	15	8	2	9
Acinetobacter spp.	1	0	0		7	1	
Anaerobic							
Gram-positive cocci	21	40	14	52	12	13	7
Bacteroides fragilis		5	4			3	7
Bacteroides melaninogenicus		11				4	
Other							
Bacteroides spp.	6	2	5	55	30	3	
Clostridium spp.	2	1	3	23		1	1
Other anaerobes		13	2	20	14	6	3
Number isolates/infection	2.76	3.62	2.88	5.76	2.77	3.8	2.3

Data from refs. [4, 25–27, 51, 63, 72]

[a] Specimens obtained by various routes, including deep ulcer swabs, curettage of the ulcer base, aspiration, or tissue biopsy

with anaerobes; however, anaerobes including *B. fragilis* may be recovered from infections that are not particularly foul smelling. Hence, clinical clues beyond the major categorization of infections are not sufficient to predict the microbiology of foot infections.

The spectrum of bacterial species recovered from foot infections, especially those that are limb threatening, can be dramatically altered by prior failed antimicrobial therapy or contact with the health care system. While *P. aeruginosa*, *Acinetobacter* species, *Enterobacter* species, and other antibiotic-resistant facultative gram-negative bacilli (some of which are resistant by virtue of extended-spectrum beta-lactamase production) are uncommon in previously untreated infections, these organisms are not infrequent isolates from infected chronic ulcers [4, 27, 30]. Similarly, MRSA may be encountered commonly in patients with chronically infected foot ulcers that have persisted in spite of multiple prior courses of antimicrobial therapy or in patients with extensive health care requirements, e.g., chronic dialysis, hospitalization for comorbid conditions, residence in skilled nursing facilities or particularly those with a prior history of infection with this organism [31]. These resistant bacteria are probably acquired nosocomially or alternatively emerge from endogenous flora during hospitalization or repetitive antibiotic treatment of patients with nonhealing foot ulcers. Accordingly, when selecting an antimicrobial regimen to treat a foot infection in a patient who has had contact with the health care system or prior courses of antibiotics, physicians should anticipate the presence of antibiotic-resistant pathogens.

The role of relatively avirulent bacteria, many of which are part of skin flora that are often isolated from cultures of specimens obtained through

an ulcer, is uncertain. *Staphylococcus epidermidis* and other coagulase-negative staphylococci have been recovered, usually in conjunction with other bacteria, from 15 to 35% of these infections and may reflect ulcer colonization. On the other hand, *S. epidermidis* has been isolated on occasion from deep tissue as the only organism suggesting these organisms may be pathogens in some patients. Enterococci, viridans streptococci, and *Corynebacterium* species, organisms that are often considered contaminants and not pathogens when isolated from skin and soft tissue infections, are among the isolates recovered frequently from polymicrobial limb-threatening foot infections. When recovered from specimens in conjunction with typical pathogens, these organisms are often disregarded as contaminants [10, 16]. Often, foot infections respond to therapy with antimicrobials which are active in vitro against the pathogens but not against these presumed contaminants [28, 32]. These observations support the designation of these organisms as contaminants; alternatively, they could indicate that with the eradication of major pathogens, host defenses and surgical debridement can control these less virulent organisms. On occasion enterococci, viridans streptococci, or *Corynebacterium* species are isolated from uncontaminated specimens and may even be the sole bacterial isolate from an infection [18]. Thus, these organisms too should not be routinely disregarded but rather interpreted in the clinical context.

Microbiologic Assessment

Clinically uninfected ulcers should not be cultured. When infection is present, a microbiologic diagnosis will usually facilitate subsequent therapy, particularly in the setting of limb-threatening infection or that occurring after failure of prior antimicrobial therapy [5, 12, 19]. While cultures of tissue obtained aseptically at surgery or purulent specimens aspirated percutaneously are more likely to contain only true pathogens, obtaining these specimens before initiating therapy is often either impractical or not feasible (no abscess present). Accordingly, before beginning antibiotic therapy the skin should be cleansed and any overlying eschar debrided. Then specimens for culture should be obtained by curettage of the necrotic base of the ulcer. Specimens should be handled and processed as both routine wound cultures and primary anaerobic cultures. As noted, specimens obtained by swabbing deep in the ulcer or from curretted tissue in the base of the ulcer may provide a reasonable assessment of infecting organisms [14, 15, 33]. If patients have been febrile recently, blood cultures should also be obtained before initiating antimicrobial therapy. With subsequent debridement during early days of therapy, specimens from necrotic purulent tissue or exposed bone should be recultured. Concurrent antimicrobial therapy may preclude isolation of susceptible organisms during effective therapy; however, resistant organisms missed on the initial cultures can be recovered from these later debridement specimens [15]. Treatment of osteomyelitis involving bones in the forefoot that will be totally resected does not require specific bone cultures, that is antibiotic therapy can be designed using the results of appropriate wound cultures. If en bloc resection of the involved bone, i.e., foot sparing amputation, is not performed, more precise microbiologic data from bone biopsy would be desirable to allow selection of optimal antibiotic for therapy [10, 16, 34]. Biopsy of abnormal bone underlying infected ulcers is generally safe and in severely neuropathic patients may not require anesthesia. Infected bone in the midfoot or posterior foot that can be probed or that lies beneath an ulcer and appears infected on imaging studies should be biopsied for culture and histopathology, ideally either surgically or using fluoroscopic guidance through a route other than the ulcer [10, 16, 34]. Here, where debridement is likely to be piecemeal, rather than en bloc resection of all involved bone, precise microbiologic data from bone is required so that optimal antimicrobial therapy can be selected. Alternatively, bone that remains unexposed after debridement and wherein osteomyelitis is not strongly suspected based on radiologic findings may not be biopsied, but rather the infection is treated as if it is limited to soft tissue. Careful clinical and radiologic follow-up of this

bone in 2–4 weeks will often resolve the question of osteomyelitis without the potential hazards of an invasive procedure.

Treatment

Debridement and Surgery

With the exception of cellulitis or lymphangitis arising from an unrecognized (or microscopic) portal of entry, infected foot lesions generally require debridement. Debridement should be done surgically rather than by chemical or enzymatic agents [35]. Urgent surgical intervention is required when patients present with foot infection complicated extensive necrosis or gangrene, crepitus or gas in tissues on imaging, necrotizing fasciitis (or pain out of proportion to findings thus suspected necrotizing fasciitis), critical ischemia, or life-threatening sepsis. For apparent non-limb-threatening infections, debridement may be limited but nevertheless allows full evaluation of the portal of entry and prepares the site for culture. Occasionally, what appeared to be a non-limb-threatening infection is discovered on debridement to actually be limb-threatening with extension of infection to deep tissue planes. Limb-threatening infection by virtue of extension to deep tissue planes requires surgical debridement [5, 12]. Early surgical intervention can reduce the duration of hospitalization and the need for major amputations [36]. Failure to decompress involved compartments and debride necrotic tissue and drain purulent collections increases the risk of amputation [5, 12, 36, 37]. Percutaneously placed drains or aspiration drainage is inadequate; rather, devitalized tissue must be resected and purulent collections drained by incision. Uncertainty about the patient's arterial circulation status should not delay initial debridement but should prompt an evaluation of arterial supply and a vascular surgery consultation. Effective debridement may require multiple procedures as the extent of tissue destruction becomes progressively more apparent. Optimal surgical treatment, that which minimizes tissue loss and results in a suitable weight-bearing foot, requires a thorough understanding of resulting foot function, avoidance of subsequent deformities that will predispose to recurrent ulceration, and recognition of the potential need for revascularization to insure healing [37]. The experience of the surgeon in this area and the availability of vascular surgery support are important in achieving optimal results [37]. If the infection has destroyed the function of the foot or if it threatens the patient's life, a guillotine amputation to allow prompt control of the infection with a subsequent definitive closure is advised [38].

Antibiotic Therapy

Antimicrobial treatment of foot infections in patients with diabetes is begun empirically and thereafter revised based upon the results of cultures, which were obtained prior to therapy and on occasion during therapy, plus the clinical response of the infection. Knowledge of the spectrum of bacteria which cause non-limb-threatening infection and limb-threatening infection, as well as the changes in these organisms that might have been induced by selected circumstances, e.g., prior antimicrobial treatment, serves as the basis for selecting effective empiric therapy. The potential toxicity of various antibiotics for individual patients and the unique vulnerability of patients with diabetes as a group must be considered. Thus, for this population with an increased frequency of renal disease, the availability of nonnephrotoxic antimicrobials with potent activity against gram-negative bacilli renders the aminoglycosides relatively undesirable and usually unnecessary. Antibiotic therapy is administered intravenously when patients are systemically ill, have severe local infection, are unable to tolerate oral therapy, or are infected by bacteria that are not susceptible to available oral antimicrobials. Some antimicrobials are fully bioavailable after oral administration, e.g., selected fluoroquinolones, clindamycin, and metronidazole, trimethoprim/sulfamethoxazole, and linezolid. When appropriate microbiologically and clinically, these could often be used in lieu of parenteral therapy initially. After control of infection,

continued therapy commonly can be effected with oral agents contingent upon the susceptibility of the implicated bacteria. For patients who require prolonged courses of parenteral therapy, e.g., for osteomyelitis, generally treatment can be provided in an outpatient setting [39].

Topical antimicrobials, including silver sulfadiazine, polymixin, gentamicin, and mupirocin, have been used to treat selected soft tissue infections; however, this approach has not been studied in foot infections. A cationic peptide antimicrobial, pexiganin acetate, used as a 1% cream applied topically was nearly as effective as oral ofloxacin in treating mildly infected foot ulcers [40]. Although antimicrobials have been applied topically to foot infections, it seems unlikely that the topical route would result in effective tissue concentrations of the antimicrobial. Accordingly, topical therapy should only be used to supplement effective systemic therapy and then with the realization that its efficacy is not established.

The potential therapeutic or prophylactic benefits of systemic antibiotic therapy in patients with uninfected neuropathic ulcers are a subject of debate. One controlled trial showed no benefit from antibiotic therapy [41]. In view of the potential adverse consequences, including colonization with resistant bacteria, antibiotic therapy is not recommended for clinically uninfected neuropathic ulcers [10, 35]. Similarly, continuation of antibiotics beyond a limited course that was sufficient to eradicate infection has not been required to accomplish the healing of ulcers that remain open [10, 17, 42].

Empiric therapy for patients with non-limb-threatening infection, many of whom can be treated as outpatients, is directed primarily at staphylococci and streptococci (Table 18.3) [10, 16, 20, 35]. Lipsky et al. demonstrated that oral therapy with clindamycin or cephalexin for 2 weeks in patients with previously untreated non-limb-threatening foot infection resulted in satisfactory clinical outcome in 96 and 86%, respectively [17]. Caputo et al. in a retrospective study reported that 54 of 55 patients with non-limb-threatening infections were improved or cured with oral therapy, primarily first-generation cephalosporins or dicloxacillin, directed at staphylococci and streptococci [19]. If patients with superficial ulcers present with more extensive cellulitis, that warrants hospitalization and parenteral antimicrobial treatment, cefazolin should be effective. However, if prior microbiologic data including known prior MRSA infection or colonization, exposure to the health care system, or other risk factors for infection caused by MRSA are present, infection caused by MRSA should be assumed and therapy should be initiated with vancomycin or another antimicrobial active against this organism. Linezolid, which is fully bioavailable when administered by mouth and thus can be given orally or intravenously, is generally active against MRSA and thus could be used for non-limb-threatening or limb-threatening foot infections [43]. Other antimicrobials active against MRSA available for intravenous administration in the setting of more extensive cellulitis include vancomycin, daptomycin, telavancin, and ceftaroline (a cephalosporin with activity against MRSA that has recently been approved by the FDA for treatment of complicated skin/soft tissue infection) [43–49]. The duration of treatment, which in the final analysis is determined by the time course of the clinical response, is usually 1–2 weeks.

Table 18.3 Selected antibiotic regimens for initial empiric therapy of non-limb-threatening foot infections in patients with diabetes mellitus

Antimicrobial regimen[a]
Cephalexin 500 mg p.o. q 6 h
Clindamycin 300 mg p.o. q 8 h
Amoxicillin-clavulanate (875/125 mg) one q 12 h
Dicloxacillin 500 mg p.o. q 6 h
Levofloxacin 500–750 mg p.o. q d
Moxifloxacin 400 mg p.o. q d
Trimethoprim/sulfamethoxazole DS, one or two tablets p.o. bid[b]
Linezolid 600 mg p.o. bid[b]

[a] Doses for patients with normal renal function

[b] Use if clinical information suggests possible methicillin-resistant *S. aureus* infection (MRSA). Trimethoprim/sulfamethoxazole may be less effective against streptococcal infection and require addition of second antimicrobial. Clindamycin is active against some MRSA

Multiple antibiotics have been demonstrated to be effective therapy in prospective treatment trials of complicated skin and soft tissue infections, many of which were foot infections. Additionally, some of these antimicrobials have been proven effective in prospective studies of foot infections, many of which have been limb threatening: amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, ticarcillin-clavulanate, cefoxitin, ceftizoxime, ciprofloxacin, ofloxacin, moxifloxacin, imipenem/cilastatin, ertapenem, linezolid, daptomycin, telavancin, and ceftaroline [4, 32, 43, 46, 50–55]. In comparative prospective (sometimes blinded) trials of treatment for limb threatening foot infections, the clinical and microbiologic response rates for the studied agents have been similar and no single agent has been proven superior to all others [10, 16, 20]. A recent review examining patients across controlled trials suggested that carbapenem therapy was associated with fewer failures compared with multiple other antimicrobials but also noted the association of MRSA infection with failed therapy [56].

In selecting empiric therapy for limb threatening foot infections, reasonable principles emerge from clinical trials and other published studies [5, 10, 12, 16, 20, 35]. The choice of agents used empirically should be based upon the known polymicrobial nature of these infections with modification, where appropriate, to address anticipated highly resistant pathogens that might have been selected in the process of prior hospitalizations and treatment (Table 18.4) [57]. Given the high prevalence of MRSA, either acquired nosocomially or the so-called community acquired variant which has become commonplace, empiric therapy for limb threatening infection should include an agent effective against MRSA. These agents will also provide therapy for infections caused by streptococci, including Group B organisms. Additionally, empiric therapy should be effective against an array of Enterobacteriaceae including potentially multidrug resistant organisms when infection occurs in a chronic ulcer which has failed to heal despite treatment with multiple antibiotics. Anaerobes, including *B. fragilis*, should be treated empirically in the more severe infection where there is tissue necrosis and gangrene. Drug selection should attempt to minimize toxicity and be cost-effective. In limb-threatening infection (but not in life-threatening infection) initial empiric therapy does not have to be effective in vitro for all potential pathogens. Broad-spectrum therapy which is active against many, but not necessarily all, gram-negative bacilli, as well as against anaerobes, *S. aureus* and streptococci when combined with appropriate debridement and good wound care may be as effective as even broader spectrum antimicrobial therapy. Adequate debridement not only shortens required duration of therapy but is also required for effective therapy.

Empiric antimicrobial treatment should be reassessed between day 3 and 5 of treatment in the light of culture results and clinical response. When patients have responded clinically and therapy is unnecessarily broad spectrum (effective therapy for the bacteria isolated could be achieved by less broad-spectrum antimicrobials with possible cost savings, avoidance of toxicity, or a reduction in selective pressure for emergence of antimicrobial resistance), treatment regimens should be simplified based on culture data [10, 16]. If a bacterium resistant to the current therapy has been recovered and yet the clinical response is satisfactory, the treatment need not be expanded. This is true particularly for less virulent organisms and gram-negative bacteria; however, it seems imprudent to ignore MRSA. Alternatively, if in the face of an isolate resistant to treatment the response to therapy is unsatisfactory, the wound should be examined for undrained deep space abscess or necrotic tissue that has not been debrided, the adequacy of arterial circulation must be assessed, and because the resistant organism might be a pathogen (rather than colonizing flora), antimicrobial therapy should be expanded to treat this isolate.

A number of regimens have been recommended as reasonable initial empiric therapy of limb-threatening infections [10, 12, 16, 20]. Because of the potentially complex microbiology of limb-threatening infection and the emergence of a multiple drug resistant phenotype among these organisms, it is difficult to recommend a single or several regimens. Some antimicrobials that have been used to treat these infections in the past are,

Table 18.4 Antibiotics for empiric therapy of limb-threatening foot infection[a]

Antibiotic agent	Comments
Vancomycin	Active against streptococci, staphylococci including MRSA
Daptomycin	Active against streptococci, staphylococci including MRSA
Linezolid	Active against streptococci, staphylococci including MRSA
Telavancin	Active against streptococci, staphylococci including MRSA
Ceftaroline	Active against streptococci, staphylococci including MRSA and many Enterobacteriaceae (not ESBL producers, *P. aeruginosa)*
Levofloxacin	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli
Moxifloxacin	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli
Amoxicillin-clavulanate	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli (not *P. aeruginosa*), also active against anaerobes
Piperacillin-tazobactam	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli including *P. aeruginosa*, also active against anaerobes
Imipenem-cilastatin	Active against streptococci and staphylococci (not MRSA) and many gram-negative bacilli including *P. aeruginosa*, also active against anaerobes. Use when considering ESBL producing organisms
Ertapenem	Active against streptococci, staphylococci (not MRSA), many gram-negative bacilli including ESBL producers (not *P. aeruginosa*), active against anaerobes. Use when considering ESBL producing organisms
Ceftriaxone	Active against streptococci, staphylococci (not MRSA), and many gram-negative bacilli (not ESBL producers, *P. aeruginosa*, or anaerobes)
Cefepime/ceftazidime	Active against many gram-negative bacilli and *P. aeruginosa* (not against ESBL producers)
Metronidazole	Only active against anaerobes

ESBL extended spectrum beta-lactamase (use imipenem-cilastatin or ertapenem). Use doses suggested for complicated skin-soft tissue infection unless concomitant infection requires higher dose. Not all agents are approved by US Food and Drug Administration (FDA) for treatment of diabetic foot infections

[a]Often may need combined therapy, especially when considering MRSA and gram-negative bacillus polymicrobial infection

because of gaps in their spectrum of activity versus the typically anticipated pathogens, are no longer considered ideal when used alone: cefuroxime, cefamandole, cefoxitin, cefotetan, ceftazidime, ciprofloxacin. In patients with limb-threatening infections arising from chronic ulcers, particularly those who have had extensive prior antimicrobial therapy or medical care, highly antibiotic resistant pathogens should be anticipated. In general, empiric regimens should combine multiple antimicrobials proven effective in the treatment of complicated skin and soft tissue infection such that coverage includes relatively resistant gram-negative bacteria and MRSA and, in selected settings, anaerobes as well (Table 18.4).

Patients with life-threatening infections, e.g., those with hypotension or severe ketoacidosis, should be treated with maximal broad-spectrum regimens. These might include a carbapenem and an agent directed against MRSA plus, if highly resistant gram-negative bacilli are anticipated, gentamicin or another aminoglycoside can be added. Emergent debridement is essential for satisfactory outcome.

The duration of antimicrobial therapy for severe soft tissue foot infection is based upon the temporal response to wound care and antimicrobial therapy. Two weeks of therapy is often effective; however, some recalcitrant infections will require longer courses of treatment [4, 5, 10, 57]. After acute infection has been controlled, antimicrobial therapy that was begun parenterally should be changed to oral therapy with comparable orally bioavailable antibiotics. Even if the ulcer has not fully healed, antibiotics can in general be discontinued when evidence of infection has resolved [10, 16]. Persistent ulcers must be managed with wound care and avoidance

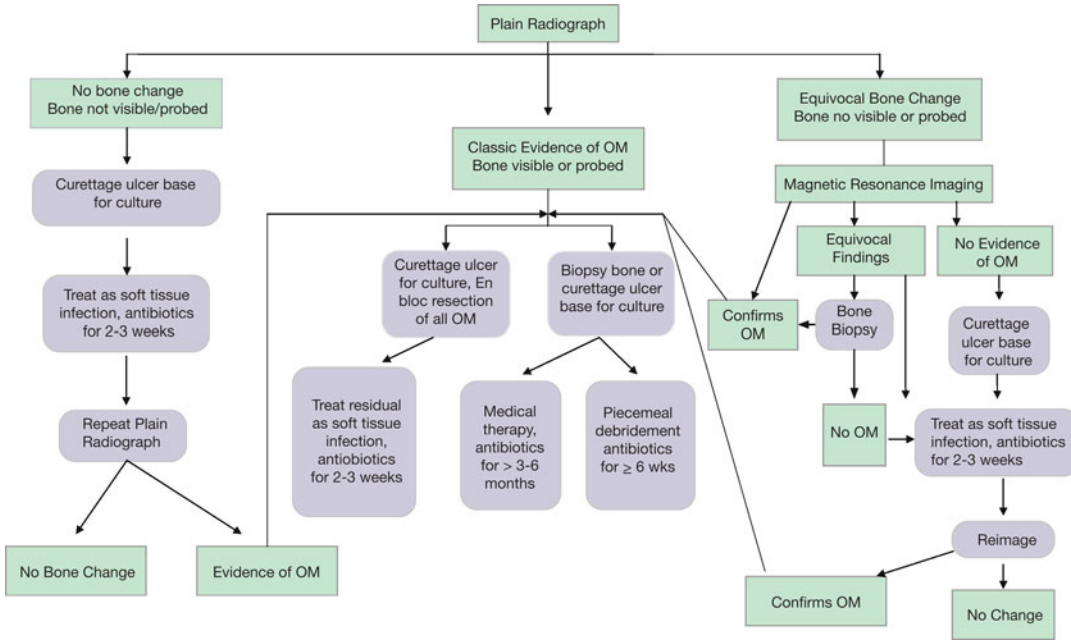

Fig. 18.1 An approach to the diabetic patient with suspected foot osteomyelitis (OM)

of weight bearing so that healing can be achieved and the ulcer eliminated as a portal for later infection. The occurrence of bacteremia, especially if remote sites are seeded, may require extended therapy. Of note, *S. aureus* bacteremia entails a distinct risk for secondary endocarditis as well as for seeding other sites such as bones, joints and the epidural space [58].

Osteomyelitis

The diagnosis of osteomyelitis is often difficult because of confounding Charcot neuroosteoarthropathy and adjacent soft tissue infection. In the diabetic foot osteomyelitis almost always results from direct extension through an overlying chronic infected ulcer. The diagnosis is reasonably certain if bone tissue (biopsy) is positive on culture and histopathology, there is purulence in bone at surgery, bone fragments are extruded, or a medullary abscess is noted on magnetic resonance imaging (MRI). Osteomyelitis is highly likely if there is visible or probe detected bone (probe to bone test) in a chronically infected ulcer, if MRI shows signs osteomyelitis, if bone tissue (biopsy) is positive by either culture or histology, but not both [6, 59]. MRI is the optimal imaging strategy for the diagnosis and determination of extent of osteomyelitis [6, 60–62]. However, the reported high sensitivity and specificity of this technique are derived from studies where the pretest probability of disease is very high and thus may be overstated if the technique is used more widely [62]. MRI imaging may be most useful in selected patients where suspicion of osteomyelitis is high but diagnostic uncertainty persists and bone biopsy is unattractive. Still the images must be interpreted with care by a knowledgeable radiologist. Nuclear isotope imaging is burdened by nonspecificity and anatomic imprecision and is not recommended [6, 61, 62]. Plain radiographs while useful as an initial step in evaluation of an infected foot, lack sensitivity and specificity. Serial radiographs over 2–4 weeks may provide evidence of osteomyelitis when in bone adjacent to an infected ulcer classic changes of infection develop in previously normal bone [6, 61, 62]. An approach to the diagnosis and treatment of the diabetic patient with suspected osteomyelitis is depicted in Fig. 18.1.

The therapy of osteomyelitis, which is one of the most debated and controversial areas in the treatment of foot infection, should coordinate antibiotic treatment with considerations of the surgical debridement of involved bone. Some reports have suggested that osteomyelitis of bones in the foot can be cured or at least arrested for extended periods with minimal debridement plus prolonged courses of antimicrobial therapy [6, 10, 16, 34, 52, 63–66]. Others have suggested that cure rates for osteomyelitis (particularly where bone destruction is evident or bone is visible or detectable by probing in an infected ulcer) will be enhanced by aggressive debridement, and even excision of all infected bone when feasible in the fore foot [5, 12, 36, 67].

A careful review of the literature on the treatment of osteomyelitis in the feet of diabetic patients concluded that no particular management strategy could be shown superior. This conclusion emerges because of heterogeneity in treated infections, diversity in the surgical approaches, biases in the selection of treatment modality, variability in antibiotic treatments and different definitions of outcome [59]. Decisions on when to use primarily medical versus aggressive debridement/resection surgical therapy in treating osteomyelitis is divided and is commonly based on physician experience. Nonsurgical management might be preferred when aggressive resection would lead to unacceptable foot dysfunction, limb ischemia precludes surgery, surgery carries excessive risk or is rejected by the patient, and osteomyelitis is limited to the fore foot (phalanges) with minimal soft tissue infection. If medical therapy fails, surgery may be required. More aggressive surgery is required if infection is life threatening or may be preferred if there is extensive bone necrosis, foot remodeling is required to correct bony prominences and improve function, the patient wishes to avoid very prolonged antibiotic therapy, or the potential toxicity of required antibiotic therapy can be minimized by aggressive surgery.

Selection of antibiotic therapy is ideally based on the precise microbiology of bone infection. Cultures from curettage of soft tissue deep in the infected ulcer overlying bone may suffice to design therapy when surgical resection of all infected bone is planned, i.e., therapy will be directed at residual soft tissue infection. However, when bone debridement will not be done or is limited, as in midfoot or calcaneous osteomyelitis, bone culture to define the microbiology is of paramount importance. Culture of soft tissue adjacent to bone does not adequately define bone microbiology [68]. Additionally, favorable outcome of therapy is more likely using antibiotics based on bone culture [65]. Adequate antibiotic therapy can be achieved by intravenous administration or the use of highly bioavailable oral agents. Specific antibiotic choices are contingent on pathogen susceptibility. Often sequential intravenous to oral therapy is used. The role of local therapy using antibiotic impregnated materials is not established [69].

Table 18.5 Duration of antibiotic therapy for osteomyelitis of pedal bone

Site/setting	Duration
Amputation with no residual infection	2–5 days after surgery
En bloc resection all infected bone with residual soft tissue infection	2–3 weeks
Residual infected bone (piecemeal debridement)	≥6 weeks after debridement
Medical therapy or after surgery with residual devitalized bone	3–6 months

[a]Adapted from ref. [10]

The duration of antibiotic treatment for osteomyelitis is based upon the amount of residual necrotic or infected bone and soft tissue (Table 18.5). If all infected bone is resected en bloc, e.g., amputation of a phalanges or phalanges and the related distal metatarsals, the residual infection has in essence been converted to a soft tissue process and can be treated accordingly, i.e., for 2–3 weeks [4, 5, 10, 12, 70]. In contrast, if osteomyelitis involves bones that cannot be resected en bloc without disruption of the functional integrity of the foot, debridement, if done at all, must be done in a piecemeal fashion. As a result, the adequacy of the debridement cannot be assured and the management strategy must be altered. In this situation pathogen-specific antimicrobial therapy should be administered for a prolonged period (at least 6 weeks) and adequate blood supply to infected tissues must be assured

[5, 10, 16, 34, 70]. Very prolonged antibiotic therapy has been used when medical cure is attempted in the setting of residual necrotic bone. The therapy has been given for 3–6 months and occasionally for a year [34, 59, 65, 66]. In every setting, the choice of a specific antimicrobial regimen and duration of therapy must be individualized and reflect not only local foot findings but also possible concomitant metastatic infection and potential adverse events.

When in spite of apparently appropriate treatment infection fails to respond and ulcers to heal, the foot should be reassessed for adequacy of arterial supply, persistence of necrotic soft tissue or bone requiring debridement, presence of a unresponsive or antibiotic resistant pathogen, or ineffective antibiotic delivery. Patient noncompliance with treatment or non-weight bearing must be considered as well. Therapy should be redesigned addressing defects found in the prior regimen.

Adjunctive Therapy

The effective treatment of foot infection is far more than the administration of antibiotics that are active in vitro against the implicated pathogens. Optimal therapy involves the integration of appropriate dressings and wound care, control of glucose metabolism, effective debridement and possibly reconstructive foot surgery. Non-weight bearing (off-loading) of neuropathic ulcers whether infected or noninfected is essential for healing. When ischemia is a limiting factor, vascular reconstruction may result in healing and foot salvage [35]. Many possible elements of adjunctive therapy are insufficiently evaluated to warrant inclusion in standard therapy. Hyperbaric oxygen therapy may facilitate healing but does not impact infection. The role of platelet-derived growth factor and bioengineered skin equivalent in healing has not been fully established. Treatment with granulocyte colony stimulating factor raises the peripheral white cell count and may accelerate slightly the control of a wound infection but has not become a standard component of care. Negative pressure dressings (vacuum-assisted closure or VAC dressings) in controlled trials have been shown to be safe and, in treating surgical wounds, to accelerate granulation tissue formation, reduce the time to wound closure, and yield a higher overall rate of wound healing [71]. Although widely used, they have not been generally recommended and their role in infected diabetic foot wounds is unclear. Topical antibiotics and antiseptics have not been demonstrated more effective than standard wound care and may cause local adverse reactions or promote emergence of resistance in bacteria. Accordingly, these have not been recommended.

Outcome

The knowledge and skills to achieve an optimal outcome in the treatment of diabetic foot infections often require the collaboration of multiple care providers, including diabetologists, infectious disease specialists, podiatrists, and vascular surgeons. With appropriate care a satisfactory clinical response can be anticipated in 90% of patients with non-limb-threatening infection and at least 60–80% of those with limb-threatening infection. Limb threatening infections may require foot-sparing amputations but salvage of a weight bearing foot is usually achievable. Vascular reconstruction, especially bypass grafts to pedal arteries which restore pulsable flow to the foot, decrease major amputations, and enable foot-sparing/foot-salvage surgery. Although the clinical science of treating diabetic foot infections has advanced significantly, challenges remain in defining optimal care. Still many foot infections could be prevented, effective therapy provided, and extremities salvaged if current knowledge was more widely applied.

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