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Diabetic Foot Infections: an Update in Diagnosis and Management

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Abstract Foot infections are a common problem in patients with diabetes and a risk factor for limb amputation. They occur as a result of skin ulceration, which facilitates penetration of pathogens to deeper tissues. The diagnosis of infection is clinical. Aerobic gram-positive cocci are the most common pathogens. Ulcers which are chronic, preceded by administration of antibiotics and hospitalization or complicated by severe infection are polymicrobial. Antibiotic therapy is initially empiric based on the severity of the infection. Definitive therapy is modified according to the results of the microbiological culture and the response to empiric treatment. The optimal duration of antibiotic therapy ranges from 1–2 weeks for mild infections to 2–4 weeks and even longer for severe infections and osteomyelitis. Surgical consultation should be sought for infections complicated with abscesses, necrotizing fasciitis or osteomyelitis. With appropriate care, infection resolves in about 80–90% of non-limb threatening and in about 60% of severe infections.

Keywords Diabetic foot infections · Diabetes mellitus · Chronic ulcers · Osteomyelitis

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Introduction

Every 20 s, a lower limb is lost somewhere in the world as a consequence of diabetes, with diabetic foot infection (DFI) playing a major role in this high incidence of amputation. DFI is also the most frequent disease-related complication requiring hospitalization and associated with increased morbidity and mortality [1]. Individuals with diabetes have at least a 10-fold greater risk of being hospitalized for soft tissue and bone infections of the foot than subjects without diabetes [2]. DFI is associated with patients' discomfort, long-term antibiotic therapy, often surgical procedures and even death. Based on recent reports in North America and Europe, 7–20% of the total expenditure on diabetes might be attributable to diabetic foot disease [3].

DFI is defined clinically as any soft tissue or bone infection below the malleoli. It includes paronychia, cellulitis, myositis, abscesses, necrotizing fasciitis, septic arthritis, tendonitis and osteomyelitis. Although most of the DFIs begin superficially, if remain untreated, microorganisms can spread contiguously to subcutaneous tissues (fascia, tendons, muscle, joints and bones). Almost 8 of 10 of non-traumatic amputations are due to diabetes; 75–85% of these amputations are preceded by a foot ulcer complicated with infection and/or gangrene [4]. Thus, early diagnosis and treatment may prevent an infection from becoming limb- or life-threatening.

Prevalence of Diabetic Foot Infections

The lifetime incidence of a person with diabetes to develop a foot ulcer is 15–25% [5]. At least half of all diabetic foot ulcers are clinically infected at the time the patient presents to clinicians [2, 6]; fortunately, most of these infected ulcers are superficial. However, in a quarter of patients, the infection will spread to the deeper tissues [1].

The true burden of DFIs is still unknown and most of our knowledge comes from retrospective studies. Lavery et al. conducted the first prospective study addressing the epidemiology of foot infections in a health care outpatient clinic [2]. They evaluated and then followed 1666 consecutive patients with diabetes for a mean of just over 2 years. Although all patients underwent regular foot assessment and were educated on foot care, 151 patients (9.1%) developed 199 foot infections. At presentation, 60.9% of the wounds were already infected. Most of these infections involved only soft tissue; yet, 20% of the patients had bone-culture proven osteomyelitis.

The Eurodiale study was a prospective observational study which enrolled 1229 subjects with diabetes presenting with a new foot ulcer in 14 foot clinics in 10 European countries [6]. At the time of presentation to the high-risk foot team, 58% of the ulcers were already infected and this percentage was increased to 85% for patients admitted to the hospital. According to the CDC, hospitalization for diabetic foot ulcer, inflammation and/or infections as a primary diagnosis was 5.7 per 1000 individuals with diabetes in 2007 [7].

Risk Factors

Diabetes has multi-factorial effects on the immune system. Impaired chemotaxis, adherence and phagocytosis of polymorphonuclear cells, dysfunction of endothelial nitric oxide response and inhibition of complement-mediated cascade account for the increased risk and severity of DFIs [8•].

An ulcer is an almost obligatory condition for the development of a DFI [2]. Loss of protective sensation and dry skin due to peripheral autonomic neuropathy predispose to skin break due to excessive pressure on a deformed foot. Once skin barrier is broken, the underlying tissues are exposed to bacterial invasion and ultimately infection. Inability of the patient to feel the pain delays recognition of a DFI; it may take up to a third longer for patients with diabetes to seek medical assistance for DFI compared to subjects without diabetes with a similar condition [9].

Peripheral arterial disease (PAD) has been found to increase approximately two-fold the risk of a wound to become infected, while the outcome of the infection is also affected by the presence of PAD [2]. Presence of ischemia may further impair the diminished inflammatory response to infection of individuals with diabetes and at the same time result in a lack of erythema and induration that are the most common clinical signs of infection. In patients with peripheral neuropathy, who have lost the ability to sense pain or warmth, the lack of erythema and induration may lead to delayed awareness of an infection [2]. At least one third of patients with both neuropathy and PAD have evidence of DFIs [2, 6].

Deeper wounds, wounds that penetrate the bone, recurrent wounds, wounds of duration >30 days and history of previous amputation are also independent risk factor for DFIs [2, 10]. Patients with the poorest general health status have also the most severe foot disease and require the most intensive therapy [6].

Classification System

Several classification systems have been developed to assess the presence of infection [1]. Each of these classifications may be used in clinical practice, and there is no evidence of superiority of one system score over the other. Recently, the International Working Group on the Diabetic Foot (IWGDF) and the Infectious Diseases Society of America (IDSA) proposed a classification system which is suitable to adequately estimate infection and guide therapy (Table 1) [1]. The IWGDF-PEDIS classification (an acronym standing for perfusion, extent, depth, infection and sensation) divides wounds to infected and uninfected (grade 1) and further divides infected wounds in grades (grades 2–4). The IDSA system divides the wounds to infected and uninfected and further divides infected wounds to those having mild, moderate or severe infection. Both systems involve clear definitions and a small number of categories, making them feasible for clinicians with limited experience with diabetic foot disease. An advantage of the IDSA classification system is that it has been validated as predicting the outcome of a DFI; increasing severity has been associated with increased risk of amputation, higher anatomic level of amputation and increased need for hospitalization [11].

Clinical Evaluation

Colonization of a diabetic wound by bacteria is not equivalent to infection. Infection is the result of pathogens invading the host tissues, causing tissue damage and inducing host's inflammatory response [12].

Symptoms and Clinical Signs

The diagnosis of a DFI is clinical and the presence of at least two local signs of inflammation: redness, warmth, pain or tenderness, swelling or purulent secretions establishes the diagnosis of DFI [1]. Presence of neuropathy or PAD may alter these signs, making the diagnosis less obvious. Diminished arterial flow may result in lack of erythema or induration, which are the presenting complain of patients that may already have lost pain perception [9]. Pain sensation may be diminished due to peripheral neuropathy. When local or systemic symptoms are weakened, presence of necrosis, discoloration, friable tissue, non-purulent secretions, fetid odor or failure of a properly treated wound to heal may indicate the presence of DFI. Fever, hypotension, increased erythrocyte sedimentation rate (ESR) and C-reactive protein level (CRP), as well as

Table 1 The IDSA and PEDIS classification of diabetic foot infections

Clinical description of infection (IDSA)	Infection severity (IDSA)	IWGDF grade (PEDIS)
No systemic or local symptoms or signs of infection	Uninfected	1
Infection:	Infected	
• At least 2 of the following items are present:		
- Local swelling or induration		
- Erythema >0.5 cm around the ulcer		
- Local tenderness or pain		
- Local warmth		
- Purulent discharge		
• Exclude other causes of an inflammatory response of the skin (e.g., trauma, gout, acute Charcot, fracture, thrombosis, venous stasis)		
Local infection involving the skin or subcutaneous tissue only (without involving of deeper tissues) and:	Mild	2
• No systemic signs or symptoms of infection		
• Erythema <2 cm* around the wound		
Infection involving structures deeper than skin and subcutaneous tissue (e.g., bone, joint, tendon) or erythema extending >2 cm* around the wound, but without systemic signs or symptoms of infection	Moderate	3
Any foot infection with the following signs of a systemic inflammatory response syndrome, as manifested by ≥2 of the following:	Severe	4
• Temperature >38 or <36 °C		
• Heart rate >90 beats/min		
• Respiratory rate >20 breaths/min or $PaCO_2$ < 32 mmHg		
• White blood cell count <12,000 or <4000 cells/μL or ≥10% immature forms		

IDSA Infectious Diseases Society of America, *PEDIS* perfusion, extent/size, depth/tissue loss, infection, sensation, *IWGDF* International Working Group on the Diabetic Foot, $PaCO_2$ partial pressure of arterial carbon dioxide

*In any direction, from the rim of the wound

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increased white blood cell count (WBC), may be absent in approximately two thirds of patients with severe foot infections [8•]. Malaise and persistent hyperglycemia may often be the only clinical manifestations, even in patients with limb- or life-threatening infections.

Severity

The evaluation of a patient with a DFI requires assessing the patient as a whole, then the affected foot and limb, and finally the wound [1]. While mild infections can be easily recognized and treated, moderate infections may be limb-threatening, since ≥50% of these patients do not manifest systemic symptoms or signs [9]. Infections with no signs of systemic toxicity, no deep abscesses, osteomyelitis or gangrene and with no or minimal extent cellulitis (<2 cm) are considered non-limb-threatening. Conversely, limb-threatening infections are those with signs of systemic toxicity, extensive cellulitis (>2 cm from the edge of the ulcer), osteomyelitis or gangrene, especially in an ischemic limb [13].

Duration of diabetes, level of glycemic control and comorbidities should be evaluated for all patients. The presence of signs of systemic inflammation (fever, chills, tachycardia and hypotension) should be promptly assessed. Determining the ankle-brachial index (ABI) is a simple, reliable, bedside procedure to estimate the presence of PAD. Loss of protective sensation can be evaluated using the 10-g monofilament in combination with another test including vibration using 128-Hz tuning fork or vibration perception threshold, pinprick sensation and ankle reflexes [14].

Most of the wounds usually require debridement. The depth and size of the wound, the extent of surrounding erythema, the quality of drainage or any evidence of bone or sinus involvement should be evaluated initially and during follow-up.

Laboratory and Imaging Approach of a DFI

Appropriate management of a DFI requires sending suitable tissue specimens for microbiological culture and performing sensitivity tests for the isolated pathogens.

Blood Culture

Blood cultures are necessary only for severe infections and especially for patients with systemic symptoms.

Wound Culture

Properly obtained wound cultures are recommended for all infected wounds prior to empiric antibiotic therapy. Since the diagnosis is clinical, the purpose of obtaining a sample for culture is to identify the most likely pathogens and their sensitivity to antibiotic. Wound cultures are not recommended for clinically uninfected wounds. Repeated cultures are not necessary, unless the patient is not clinically responding to therapy or the pathogen is more likely to represent contamination.

Three techniques are commonly used to obtain a wound culture: swabs, tissue biopsy or needle aspiration.

Superficial culture obtained with cotton swabs is common in the clinical setting, since it is a practical, less invasive and economic method. The major concern is that swabs do not always reflect the true microbiology present in the deeper tissues; they yield a mixture of pathogens, colonizing organisms and contaminants, and can miss anaerobic and some fastidious bacteria [15]. If swabs are the only available specimens, attention should be paid to the procedure followed. The wound should be debrided to access viable tissues, thoroughly cleaned with sterile gauze soaked in sterile saline, and then, swab culture for both aerobes and anaerobes should be obtained [16].

Biopsy of deep tissues, obtained at surgery or after scrapping the base of a debrided ulcer (curettage), usually reveals the true pathogens. Needle aspiration of purulent secretions involves inserting a needle into the tissue to aspirate fluid. This technique will obtain microbes below the surface of the wound; yet, it is invasive and may be painful [16]. Both tissue biopsy and needle aspiration are considered more reliable techniques, since the isolates are more likely to be pathogens than contaminants. Any specimen should be collected in sterile containers and sent to the laboratory with clinical information.

Bone Biopsy

Obtaining a bone specimen for culture will provide the histopathological and microbiological evidence of osteomyelitis, as discussed in the osteomyelitis section. Bone biopsy will also help to identify the responsible pathogens and their sensitivity to antibiotics.

Laboratory Tests

Although a diabetic foot infection is diagnosed mainly clinically, attending the general metabolic state of the patient is essential [17, 18]. Basic serum chemistry and hematology testing, such as hematocrit, serum creatinine, blood urea nitrogen and estimated glomerular filtration rate, should be evaluated in order to assess antibiotic dosage and patient's metabolic condition. Unfortunately, no blood test can definitely diagnose a DFI. Markers of inflammation, such as ESR, provide additional support for the diagnosis, especially in the presence of osteomyelitis; yet, they should never be relied on alone to make a diagnosis [19]. Elevated WBC count is not consistently reported in studies, even in the case of osteomyelitis [20]. In a retrospective study of patients with diabetes admitted to hospital with acute foot infections and osteomyelitis, an elevated WBC count was absent in approximately half of the patients with osteomyelitis [20]. The ESR is more diagnostically useful of a DFI, in particular of osteomyelitis. A level of ESR >70 mm/h increases the possibility of osteomyelitis [21]. Plasma levels of CRP and procalcitonin have accurately distinguished clinically uninfected ulcers from those with mild or moderate infections and may be predictive for the presence of osteomyelitis; yet, they should be used solely as supportive data [22]. Currently, no cost-effectiveness data exist regarding the value of inflammation markers in the diagnosis and monitoring of DFI.

Imaging Techniques

Radiographic evaluation is necessary for all patients with a new DFI [1]. Plain radiographs can show subcutaneous gas, foreign bodies, fracture, changes indicating neuro-osteoarthropathy (Charcot foot) or cortical erosions suggestive of osteomyelitis [13]. Further imaging studies such as magnetic resonance imaging, bone scans and radiolabelled WBC scans are needed only for the diagnosis of osteomyelitis or when soft tissue abscess is suspected.

Microbiology

Many previous studies have reported that DFIs are usually mixed infections, caused by 3–5 species, including aerobic gram-positive cocci, gram-negative and anaerobes [23–25].

In Western developed countries, acute infections in patients with no recent administration of antibiotics are usually monomicrobial, with aerobic gram-positive cocci being the predominant microorganisms. Gram-positive aerobic bacteria account for two thirds of overall isolates, with *S. aureus* being the commonest (~30%) [26]. *S. epidermidis* and *S. haemolyticus*, *β-hemolytic streptococci* (groups A, C, G and especially group B) and *Enterococcus faecalis* are also frequently isolated [27].

Gram-negative aerobic bacteria (mainly *Enterobacteriaceae* spp., *Pseudomonas aeruginosa* and *Acinetobacter* spp.) are less common and are found mostly in patients with chronic, previously treated wounds. Recently, epidemiological surveys from less-developed countries with warm climates have reported a

considerably higher prevalence of gram-negative rods, especially *Pseudomonas aeruginosa.* The use of poor quality footwear, a higher incidence of non-prescription antibiotic agents, foot sweating, frequent foot soaking and suboptimal hygiene may account for this geographical difference [28].

Deep and chronic infections, especially those in patients who have recently been treated with antibiotics, are usually polymicrobial. Culture obtained from these wounds yields 3–5 isolates, including *Enterococci*, *Enterobacteriaceae*, obligate anaerobes (*Peptostreptococcus, Clostiridium*, *Bacteroides*, *Fusobacterium* and *Corynebacterium* spp.), *Pseudomonas aeruginosa* and fungi (mainly *Candida* spp.) [8•].

Obligate anaerobes are never the sole bacterial species isolated; they are usually suspected in the presence of necrotic or ischemic tissues or fetid odour. Yet, they are not associated with any specific clinical findings or worse outcomes, and the clinical importance of these findings is unclear [29].

The increased incidence of multidrug persistent organisms (MDRO) over the last decade, such as extended-spectrum β-lactamase (ESBL)-producing gram-negative rods or methicillin-resistant *S. aureus* (MRSA), is of major concern. Infection with MDROs has been inconsistently associated with increased hospital stay duration, additional morbidity and raised rates of amputation [30]. Previous hospitalization has been shown to be the most significant risk factor for MDRO infection, suggesting that the MDROs are probably required in the hospital by cross-transmission [31]. Osteomyelitis, neuroischemic ulcer, previous surgical procedures, long duration of non-healing wounds with prolonged or broad-spectrum antibiotic therapy predispose to colonization and infection by antibiotic-resistant species [31].

The most frequently isolated MDRO is MRSA. The incidence of MRSA in infected foot ulcers is reported to be as high as 15–30% [30]; up to 40% of *S. aureus* isolates may be MRSA [26]. Most of the studies report that MRSA infection is associated with prior antibacterial treatment, long-standing ulceration and prior hospitalization [26, 30].

Lately, gram-negative organisms that produce ESBLs or carbapenemases and even MRSA with intermediate resistance to vancomycin (VISA) are the most worrying problem regarding antibiotic resistance [28].

Osteomyelitis

Osteomyelitis is present in approximately 20–66% of cases of DFI and dramatically raises the likelihood of lower-limb amputation [32]. Diabetic foot osteomyelitis (DFO) rarely occurs as a result of hematogenous dispersion. Almost all cases result from contiguous spread of infection of the adjacent soft tissue of an ulcer [33]. Therefore, the affected bones are usually adjacent to areas where ulcers are most common (phalanges, metatarsal heads and calcaneus).

Clinical Evaluation

Underlying osteomyelitis should be suspected when an ulcer overlying a bone fails to heal after 6 weeks of proper care or when a toe is swollen and erythematous (“sausage toe”) [33]. Any ulcer in which bone is either visible or can be palpated with a probe-to-bone test is also likely to be complicated with osteomyelitis. A wound that penetrates to bone or joint, a history of previously healed foot ulceration and the development of recurrent or multiple wounds have also been found to be independent risk factors for DFO [32].

Microbiology

Since DFO generally occurs by contiguous spread, the causative pathogens are similar to those isolated from complicated soft tissue infections. *S. aureus* and *Streptococcus* spp. account for about 60% of the isolated agents and gram-negative for up to 25%. Anaerobes are less common compared to soft tissue infections.

Laboratory and Imaging Approach of DFO

Diagnosing DFO is often misleading, since clinical signs may be diminished and radiographic evidence may be inadequate. Yet, the diagnosis of DFO should be pursued aggressively as it is a limb-threatening condition. Recently, the IWGDF proposed a consensus scheme for the diagnosis of DFO. This expert opinion categorizes the diagnosis to 4 categories, as definite, probable, possible and unlikely, based on combinations of clinical signs, laboratory results such as elevated ESR and positive bone cultures, and imaging techniques such as plain radiographs and magnetic resonance imaging [33]. Proposed criteria for diagnosing osteomyelitis in diabetic foot are shown in Table 2.

Bone Biopsy

Biopsy of a bone specimen at the time of surgery or under fluoroscopic or CT guidance is considered the gold standard of diagnosis. In an insensate foot, bone biopsy can be performed with little or no anesthesia and the rate of complications is low. The sample is then subjected to both histopathologic and microbiological examination, which will provide reliable data on the organism responsible for the infection and will also determine the narrow-spectrum targeted antimicrobial therapy. Yet, bone sampling is not routinely performed in many specialist centers, as there may be clinical difficulties for the procedure. In addition, recent reports yield significant doubts about whether bone biopsy will provide an improvement in clinical outcome compared with empirical therapy. Thus, bone biopsy is more strongly recommended when the diagnosis remains uncertain despite clinical and imaging

Table 2 Proposed criteria for the diagnosis of osteomyelitis in diabetic foot

Category	Probability of osteomyelitis	Criteria
Definite	>90%	Bone sample with positive culture and positive histology
		Or
		Purulence in bone found at surgery
		Or
		Atraumatically detached bone fragment removed from ulcer
		Or
		MRI showing intraosseous abscess
		Or
		Any 2 probable criteria
		Or
		1 probable and 2 possible criteria
		Or
		Any 4 possible criteria
Probable	51–90%	Bone sample with positive culture but negative or absent histology
		Or
		Bone sample with positive histology but negative or absent culture
		Or
		Visible cancellous bone in ulcer
		Or
		MRI showing bone edema with other signs of osteomyelitis
		Or
		Any 2 possible criteria
Possible	10–50%	Visible cortical bone in ulcer
		Or
		Probe to bone positive
		Or
		Non-healing wound despite adequate offloading and perfusion for >6 weeks
		Or
		Ulcer of >2 weeks duration with clinical evidence of infection
		Or
		Plain radiography showing cortical destruction
		Or
		MRI showing bone edema or cloaca
		Or
		ESR > 70 mm/h with no other plausible explanation
Unlikely	<10%	No signs or symptoms of inflammation and normal plain radiography and ulcer present <2 weeks or absent and any ulcer present is superficial
		Or
		MRI normal
		Or
		Normal bone scan

MRI magnetic resonance imaging, *ESR* erythrocyte sedimentation rate

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evaluation; cultures of soft tissues suggest absence, multiple or antibiotic-resistant organisms; the patient fails to respond despite empiric or culture-directed therapy; the potential antibiotic agent has a high potential for selecting resistant

organisms [1]. When possible, antibiotics should be discontinued for at least 48 h and ideally for 14 days before bone biopsy [34].

Laboratory Tests

A value of ESR >70 mm/h has been shown to have a positive predictive value of 100% and a negative predictive value of 83% for the diagnosis of osteomyelitis [35]. Elevated WBC and CRP have also been evaluated. Yet, overall, no blood test seems adequate to support the definite diagnosis of DFO.

Probe-to-Bone Test

Palpation of bone with a sterile, blunt, metal probe (probe-to-bone test) is a simple procedure to detect osteomyelitis, based on the concept that if the probe can reach the bone, so can infectious bacteria [36]. Yet, the accuracy of that rather feasible to perform test in predicting or excluding osteomyelitis is directly related to the prevalence of osteomyelitis, with higher positive predictive values in populations with the highest prevalence. In the presence of an infected wound, a positive prone-to-bone test is highly suggestive of osteomyelitis, but a negative test does not exclude the diagnosis. Conversely, in an apparently uninfected wound in a patient of low risk, a negative probe-to-bone test can practically rule out osteomyelitis [37•].

Imaging Techniques

All patients with a long-standing or deep ulcer should have a plain foot radiograph taken to detect the presence of foreign bodies, bone deformities, infection and arterial calcification. Unfortunately, the typical radiographic triad of osteomyelitis (demineralization, periosteal reaction and bone destruction) appears when 30–50% of the bone is destroyed. Thus, it may take 2–3 weeks for DFO to become radiologically apparent. Changes in radiological appearance after a 2–4-week interval are more likely to predict the presence of osteomyelitis than a single image [38].

Several studies compare the effectiveness of radionucleotide bone scans for the diagnosis of DFO. Technetium 99 m phosphate bone scan has a sensitivity of 81%, which is higher than plain radiographs, but a low specificity (only 28%), due to the inability to distinguish osteomyelitis from other inflammatory processes, in particular acute Charcot [39–43].

Magnetic resonance imaging (MRI) is considered the most useful imaging study for diagnosing DFO. Compared to radionucleotide bone scans, MRI scans enable the accurate definition of the anatomic location and extent of osteomyelitis, as well as any soft tissue infection. In a meta-analysis of 16 studies conducted to determine the diagnostic value of MRI in a total of 485 patients suspected of having osteomyelitis of the foot or ankle or who had foot infection, the sensitivity of MRI was high and ranged from 77 to 100% and the specificity from 40 to 100% [44]. The lower specificity is attributed to the inability of MRI to distinguish between infection and acute Charcot foot [41, 44].

Radiolabelled WBC scan is probably superior to MRI in detecting clinically unsuspected osteomyelitis in diabetic foot ulcers and in distinguishing between osteomyelitis and acute Charcot [41, 45]. Radiolabelled WBC are usually not taken up by healthy bone; therefore, a negative result strongly indicates the absence of osteomyelitis, but a positive result requires further study [42, 46]. Preliminary data suggest that fluorodeoxyglucose (FDG) positron emission tomography/computed tomography may be helpful in the diagnosis of DFO and may enable the differentiation between osteomyelitis and acute Charcot foot [47]. Fluorine^{18} FDG is rapidly taken up by high-glucose-using inflammatory cells in osteomyelitis [39]. In acute Charcot foot, on the other hand, only a low-grade diffuse FDG uptake is observed that is clearly distinguishable from the higher uptake observed in sites with osteomyelitis [47].

Treatment

Treating DFIs aim to prevent the spread of infection to deeper tissues and especially into bone, which may evolve into a limb- or even life-threatening condition.

General Measures

Optimization of glycemic control is important for the management of DFIs, as hyperglycemia impairs leukocyte function.

Debridement of the ulcer in combination with off-loading is important for healing. Debridement removes necrotic tissues that predispose to the development of anaerobic pathogens, while it exposes any remaining anaerobes to oxygen enhancing their eradication. After debridement, the wound should be examined with a sterile metal probe to assess the depth and the presence of foreign materials, abscesses, sinus tract or exposed bone [12].

Indications for Hospitalization

Patients with severe infection need to be hospitalized. The majority of patients with mild infections and most of patients with moderate infections can be treated as outpatients. Outpatient care requires that the patient is reliable, has good home support and will be willing to be re-assessed within 72 h or earlier if the infection worsens. Hospitalization may be needed for patients that will not adhere to therapy or have no family or social support, or have metabolic instability (hyperglycemia, electrolyte imbalance or acute kidney injury).

Antimicrobial Therapy

Antimicrobial therapy should be reserved for wounds that are infected; there is no evidence to support that administration of antibiotics in uninfected wounds can prevent infection or enhance ulcer healing [37•].

Route of Therapy

Almost all mild and most of the moderate infections can be treated with oral antibiotics. Oral antibiotics are more convenient, have fewer side effects and are less expensive. Most of the currently used oral agents are well-absorbed and achieve adequate serum and tissue levels.

Broad-spectrum parenteral therapy is required for patients with severe infection. Parenteral antibiotics may also be required when patients cannot tolerate oral antibiotics or when the pathogens are resistant to oral agents. Once the patient is stabilized and the infection is resolving, most patients can be switched to oral therapy [37•].

Topical Antimicrobial Therapy

Topical antibiotic therapy offers several advantages over systemic administration. It allows high concentration of antibacterial agent at the site of the infection, decreases the induction of bacterial resistance and reduces the incidence of systemic toxicity and side effects [48]. Antiseptics like povidone-iodine are not recommended for open wounds because they are cytotoxic for the injured tissues [48]. Silver, neomycin, polymixin B, gentamycin and mupirocin have been used for soft tissue infections at other sites, but there are no published data for DFIs. There is also no evidence to recommend the use of silver-containing dressings or topical silver agents for infected wounds [49]. Pexiganan acetate cream might be an effective alternative to oral ofloxacin for mild DFIs and might reduce the risk for selecting antimicrobial-resistant bacteria [50].

Choice of Antibiotic Regimen

Before choosing an antimicrobial agent, the results of the microbiological tests must be interpreted on the basis of clinical evaluation of the infection. Initial antibiotic therapy is usually empirical, based on the severity of the infection and the knowledge of the local microbial epidemiology. The regimens selected should cover the most common pathogens and then be modified according to the results of the cultures. Even in an ischemic foot, antibiotics play an important role in preventing further spread of the infection. An empiric therapy should include an agent against aerobic gram-positive cocci (*S. aureus* and *Streptococci*) such as amoxicillin-clavulanate and clindamycin, but it may be broadened to include gram-negative bacilli such as *Enterococcus* spp. if the infection is severe or if the patient has failed to respond to narrower spectrum therapy [29]. If the patient has risk factors for MRSA infection, an agent active against MRSA should be added, such as clindamycin, trimethoprim/sulfamethoxazole and linezolid. Empiric antipseudomonal treatment is not necessary, unless the patient has risk factors for such an infection, like frequent exposure of the foot to water, warm climate, abundant maceration and high local prevalence of *Pseudomonas* infection [8•].

Once culture and sensitivity results are available, it is preferred to switch to narrower spectrum agents. When cultures yield multiple organisms, a decision should be made about which isolate needs to be covered. If the infection is improving, there may be no need to change treatment, even if some or all of the agents are resistant to the agents prescribed. If the infection is worsening, therapy should be broadened to cover all isolated pathogens, MRSA, resistant gram-negative rods, anaerobes or fastidious organisms, such as *Mycobacterium tuberculosis*. In these cases, it is also recommended to obtain new specimens for culture.

Several antibiotics have been reported to successfully treat DFIs [1, 51, 52]. Overall, no drug or combination of agents or route of administration has been shown to be superior to other in soft tissue or bone infections [52]. At standard doses, most β-lactam antibiotics achieve relatively low, but likely therapeutic tissue levels, whereas clindamycin, fluoroquinolones, linezolid, rifampin and co-trimaxozole have shown satisfactory penetration to bone, synovia, bioflim and necrotic tissue [28]. Table 3 shows a recommended empiric therapy according to the severity of the infection [53]. Consultation with an infectious disease specialist is imperative in choosing antibiotic regimen.

Duration of Antibiotic Therapy

There are no proven laboratory tests or imaging techniques to determine when antibiotic therapy should be discontinued. Thus, optimal duration of antibiotic therapy is not well documented [52]. For mild to moderate infections, 1–2-week course is usually effective, while for more severe infections, 3 weeks is usually sufficient [37•]. The duration of therapy can be shorter once the infection is resolved, even if the wound has not completely re-epithelialized. More extended treatment may be needed for immunocompromised patients, for wounds that are poorly perfused, for deep and large wounds, for osteomyelitis or for patients with implanted foreign body at the infection site.

Surgical Intervention

Surgical therapy should be considered early in all patients with moderate or severe DFIs. Surgical intervention may range from debridement of necrotic tissues, drainage of abscesses, opening infected compartments to major amputation. DFIs complicated with gas in the deeper tissues, abscesses or

Table 3 Proposed empiric therapy for the management of diabetic foot infections

Severity of the infection	Route	Antibacterial agent and dosage[a]	Comments
Mild/Moderate[b]	PO	Amoxicillin/clavoulanic acid 500/125 mg q8h or 875/125 mg q12h	Penicillins are the only oral agents effective against *Enterococci*. Anaerobic coverage.
		Cephalexin 500 mg q8h	
		Clindamycin 300 mg q6h	For patients with known allergy to penicillins. Effective for MRSA, but not as monotherapy. Associated with *Clostiridium difficile* diarrhea.
		Dicloxacillin or flucloxacillin 500 mg q6h Ofloxacin[c] 400 mg q12h	Oral agent of choice for MSSA.
		Ciprofloxacin[c] 500 mg q12h	Modestly active against Gram-positive aerobic cocci and anaerobes. Should be used in combination with clindamycin and not as monotherapy.
		Levofloxacin[c] 500 mg q12h or q24h	Suboptimal against *S. aureus*.
		Moxifloxacin 400 mg q24h	Broad spectrum, obligate anaerobic coverage.
		Co-trimoxazole 960 mg q12h	Effective for many MRSA and gram-negatives.
Moderate/Severe[b]	IV until stable, then switch to oral equivalent if possible	Clindamycin 450–600 mg q6h + Ciprofloxacin 400–750 mg q12h Ampicillin/sulbactam 3 g q6h	Effective for MRSA, but not as monotherapy.
		Ticarcillin/clavulanic acid 3.1 g q4-6 h	Broad spectrum coverage.
		Piperacillin/tazobactam 4.5 g q6h	Broad spectrum coverage, including *Pseudomonas*.
		Ceftriaxone 1 g q12h or Ceftazidine 2 g q 8 h + Clindamycin 450–600 mg q8h or Metronidazole 500 mg q8h	Third generation cephalosporins are less active against staphylococci.
		Ertapenem 1 g q24h	Broad-spectrum, including anaerobes, but not *Pseudomonas*.
		Fluoroquinolone + metronidazole 500 mg q6h	
Life-threatening	IV	Imipenem/cilastatin 500 mg q6h	Not effective against MRSA. Should be considered if ESBL pathogens are suspected.
		Piperacillin/tazobactam 4.5 g q6h + gentamicin 1.5 mg/kg q8h	Broad spectrum coverage, including *Pseudomonas*. Aminoglycosides are difficult to dose in patients with renal dysfunction.
		Vancomycin 1 g q12h + gentamicin 1.5 mg/kg q8h + metronidazole 500 mg q8h	Teicoplanin 400 mg initially and then 200 mg q24h, or linezolid 600 mg q12h, or daptomycin 4 mg per kg q24h can also be used instead of vancomycin. Aminoglycosides are difficult to dose in patients with renal dysfunction. Effective against MRSA, *Pseudomonas, Enterobacteriacae* and anaerobes.

PO oral, *IV* intravenous, *MRSA* methicillin-resistant *S. aureus*, *QID* 4 times a day, *MSSA* methicillin sensitive *S. aureus*, *TID* 3 times a day, *ESBL* extended-spectrum β-lactamase

[a] Modified dosages based on renal function and body mass. Similar agents to those listed can also be used

[b] Consider adding an agent against MRSA if the patient has risk factors for MRSA infection (e.g., severe infection, increased prevalence, evidence of infection or colonization with MRSA)

[c] Oral fluoroquinolones reach adequate serum levels even in diabetic patients with gastroparesis

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necrotizing fasciitis require urgent surgical management [1]. The optimal time for surgery is difficult to be defined. Early debridement by an experienced surgeon results in better outcomes and limb salvage. Every effort should be made to avoid

amputation. Extensive gangrene, long unsuccessful course of therapy, life-threatening soft tissue infection and extensive osteomyelitis are indications for lower limb amputation [12]. When amputation is needed, the goal is to perform the most distal amputation that will promote healing and patient's return to optimal function [13]. A higher-limb amputation should be avoided unless the limb is non-viable, functionally useless or affected by a life-threatening infection (e.g. gas gangrene or necrotizing fasciitis) [18].

Patients with limb ischemia should be evaluated by a vascular surgeon. Patients with noncritical ischemia (ABI 0.5–0.9) can be treated successfully without vascular procedure. If urgent revascularization is required for a critically ischemic limb, it should be performed as early as possible [18].

Non-antibiotic Treatment of DFIs

Over the last few years, several studies have addressed the use of stimulating factors and adjunctive interventions to improve the outcome of DFIs. These interventions include the use of bioengineered skin equivalents, growth factors, granulocyte colony-stimulation factor (G-CSF), hyperbaric oxygen therapy or negative pressure wound therapy. In a meta-analysis of randomized-controlled trials, adjunctive therapy with G-CSF did not appear to increase the likelihood of resolution of the infection, wound healing or duration of systemic antibiotic therapy [54]. Yet, it seemed to be associated with shorter hospital stay and reduced rates of amputation, especially in patients with limb-threatening infections [54]. Hyperbaric oxygen therapy may facilitate the healing of chronic foot ulcers, but it has no effect on promoting healing of DFIs [55]. The available evidence does not support the value of platelet-derived growth factors, stem cell therapy or vacuum-assisted negative-pressure therapy in addition to conventional therapy for the resolution or prevention of infection [28].

Treating Osteomyelitis

While many cases of DFO require or may benefit from surgical debridement or resection of the bone, the current available data do not support the inferiority of surgical therapy over medical and the opposite [37•]. A variety of limb-salvaging surgical interventions have been described. The combination of early surgery and antibiotics versus antibiotics alone has been associated with a significant reduction of major amputation. Yet, no final conclusion can be drawn from previous studies [52].

Ideally, the antibiotic therapy should be based on the sensitivity test of bone culture. If this is not possible, the therapy should be empirical and a regimen that covers *S. aureus*, such as clindamycin, should always be included [37•]. The available literature does not demonstrate a significant advantage of any antibiotic agent, route of administration or duration of therapy [56]. Although treatment of osteomyelitis has traditionally been initially parenteral, there is no strong data supporting this approach [37•]. Fluoroquinolones, rifampicin (always companied with another agent), clindamycin and co-trimoxazole are oral agents with good tissue and bone bioavailability. For patients in whom the bone has been removed surgically, a shorter course of antibiotic therapy (2–14 days) may be adequate [52]. Extending post-debridement antibiotic therapy beyond 6 weeks or giving parenteral treatment longer than 1 week does not appear to increase remission rate [37•]. There is no strong evidence for the effectiveness of adjunctive therapies [37•].

Treatment Outcome

With appropriate treatment, infection resolves in 80–90% of non-limb-threatening infections and in 50–60% of more severe infections. Rates of lower limb amputation may reach 50–60% in extensive infections and in medical centers with low experience [57]. The presence of osteomyelitis, limb ischemia, systemic infection and gangrene or of an unskilled surgeon is associated with poor outcome [18]. Unfortunately, DFI may relapse in 20–30% of patients, especially in those with underlying osteomyelitis [51]. It is not always feasible to suggest that osteomyelitis has completely been cured. Decrease of elevated inflammatory markers (especially ESR), resolution of the overlying soft tissue infection, reconstruction of destroyed bone on plain radiograph and healing of any wound have been proposed as suggestive of clinical response. Because DFO recurrences are common, remission for at least a year is considered as a treatment success and finally cured foot [37•].

Conclusions

DFIs represent a strong risk factor for hospitalization and amputation. Diagnosis should be based on clinical signs and symptoms supported by a combination of blood tests, microbiological findings and imaging. Yet, the key recommendation is not to use newer expensive therapies, but the early prevention. Removing patients' shoes and socks and examining for detection of loss of protective sensation are sufficient to recognize a foot at-risk. Patient and clinician education, intensive glycemic control and regular foot examination are more promising in reducing the incidence of diabetic foot and DFIs.

Compliance with Ethical Standards

Conflict of Interest Pinelopi Grigoropoulou, Ioanna Eleftheriadou, Edward B. Jude, and Nikolaos Tentolouris declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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