Treatment of musculoskeletal infections of the foot in patients with diabetes

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The incidence of diabetes, diabetic neuro-vasculopathy and as a result, diabetic foot ulceration is a growing problem all over the world. Diabetic foot ulcers are the most common gateways to foot infection. More than 50% of ulcers will become infected at some stage. The authors review the epidemiology, risk factors, pathophysiology, diagnosis, prevention and treatment of diabetic foot infections, including osteomyelitis. Medical and surgical, local and general treatment – including the empirical and evidence-based use of antibiotics – are thoroughly reviewed.

Keywords: antibiotic treatment, diabetic foot infection, diagnosis, epidemiology, medical treatment, microbiology, prevention, risk factors, surgical treatment

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Diabetes mellitus is a major and growing health problem with an estimated 150 million people affected by the disease worldwide, with a twofold increase in this number predicted over the next two decades [1]. The combination of neuropathy, vasculopathy, and impaired host defence mechanisms makes patients with diabetes vulnerable to foot infections. A high degree of clinical suspicion and vigilance is necessary for early diagnosis of pedal infections and their differentiation from an uninfected foot ulcer or sterile inflammatory conditions, such as Charcot joint or gouty arthritis [2].

Epidemiology

Foot infections are frequent complications of diabetes mellitus accounting for 28% of diabetes-related hospital admissions [3]. Lavery and colleagues evaluated 1666 patients with diabetes and noted an annual incidence of foot infection of 36.5 per 1000 [4]. Ulceration is the most common precursor of diabetic foot infection; the annual incidence of new diabetic foot ulcers is 2 to 7% [4–6]. More than half of all lower extremity ulcers become infected [4]. Whilst most infections are superficial, approximately 25% spread from the skin to deeper subcutaneous tissues [7]. In these patients with with diabetic foot ulcers, 7 to 13% develop osteomyelitis [6,8], and 15% of these require amputation [6].

Approximately half of all lower extremity amputations (LEA) are performed on the 5% of the US population with diabetes [9,10]; these figures are similar in Europe [11,12]. The rate of LEA in the diabetic population is 7–15 times higher than in non diabetic individuals [9,10]. Foot ulceration and subsequent infection of diabetic patients is the indication for LEA in more than 50% of patients requiring this operation [13–16]. In a Swedish study including 223 diabetic patients with severe foot infections amputation was more common in patients with combined infection (osteomyelitis and deep soft tissue infection, [62%] compared with those who had osteomyelitis [37%] or a deep soft tissue infection only [30%]) [17].

Total direct cost of the treatment of infected ulcers not requiring amputation is approximately $17,500 (in 1998 US$), whereas the cost for LEAs is approximately $30,000–33,500 depending on the level of amputation [18]. It has been estimated that with appropriate knowledge of risk factors and treatment by a multidisciplinary team, over 50% of foot and leg amputations in diabetic patients can be prevented [15,19–21].

Several recent local and international initiatives are attempting to reduce the burden of diabetic foot problems. One of the major goals of the European St Vincent Declaration on Diabetes is the reduction of amputations by 50% by 2010 [22].

Currently, there are only 5 years remaining until 2010, and it is questionable whether reduction of amputation by 50% can be achieved within this established deadline. There is certainly room for improving both diagnosis and treatment of diabetic foot infections [23], which is also the intention of this paper.

Risk factors & pathophysiology of diabetic foot ulcers & infection

Ulceration of the foot is the most common preceding event of infection. Neuropathy has been shown to be a major risk factor both for ulceration and infection. In a 24 month follow-up study of 1666 diabetic patients, 38.6% with peripheral neuropathy developed ulcers [4]. Sensory neuropathy leads to the loss of protective sensation of pain, pressure, heat and proprioception. Minor

repetitive trauma, and sometimes even major tissue damage may ensue unnoticed [24]. Autonomic neuropathy may result in dry skin with cracking and fissuring, creating an excellent portal of entry for bacteria [24]. Motor neuropathy [24] causes crural muscle atrophy and/or intrinsic muscle wasting, leading to foot deformities. Deformities, reduced mobility of the joints, calluses and overweight increases pressure on the foot soles. Peak foot pressures may be several-fold higher in patients with diabetes than those in nondiabetic individuals [25]. Autonomic dysfunction, vascular fragility, ischemia, and reduced muscular activity all result in an increase of extracellular fluid, resulting in diffuse swelling and oedema, characteristic of advanced diabetes [24]. Oedema of different compartments of the foot increases intracompartmental pressure and may amplify the ischemic cascade [26].

Risk of foot ulceration is proportional to the product of pressure & time

The risk of peripheral vascular disease (PVD) in diabetic patients is approximately twofold and this number increases with the patient's age and duration of diabetes [27]. Occlusive changes may be variable at different levels of the limb, with significantly diminished blood pressure of the toes. Periwound cutaneous perfusion is one of the critical factors for impaired wound healing [28]. PVD is associated with 62% of nonhealing foot ulcers and is the predisposing factor in 46% of amputations [13]. Several defects in host immune defence are more common in patients with diabetes than in nondiabetic individuals. These include impairment of polymorphonuclear leukocyte function, such as migration, phagocytosis, intracellular killing, and chemotaxis [24,29]. Some evidence suggests that cellular immune responses are also reduced [24]. Patients with diabetes have a higher incidence of superficial fungal infections [30]. These infections frequently disrupt the skin's integrity, allowing the entrance of bacteria. Furthermore, the unique anatomy of the foot contributes to the potential severity of infections. The structure of the various compartments, tendon sheaths, and neurovascular bundles tend to favor the proximal spread of infections.

Progress of infection

When the protective layer of the skin has been breached bacterial invasion and infection may progress quickly. In the presence of virulent organisms infection may progress from superficial to deep, causing limb-threatening infections, despite adequate medical intervention [31,32]. Infections may spread from one compartment to another at their proximal calcaneal convergence, or by direct perforation of septae. Lateral or dorsal spread is a late sign of infections [7].

Dorsal foot cellulitis starts on the toes at the base of nails or in the web space. Deep plantar space infections have their origin most frequently in the web space and nail bed; prognosis is usually good if treated early. Infections of the central plantar space results in a loss of skin creases and loss of the longitudinal arch of the foot. Complications of central space infection include gangrene of the toes due to compromised arterial flow in the arterial arch or the digital branches, causing ischemic necrosis of the intrinsic foot muscles, suppurative tendinitis, arthritis and sepsis [33].

Pedal ulcers are portals of entry for infection and directly overlie more than 90% of cases of pedal osteomyelitis [34]. Bacteria gain access to bone by contiguous spread, entering from overlying soft tissue and penetrating the cortex before involving the marrow [35]. The bones of the forefoot are usually involved, particularly the first digit [35].

Diagnosis & classification of diabetic foot infections

Diabetic foot infection includes paronychia, cellulitis, infected foot ulcer, septic arthritis, tenosynovitis, myositis, fasciitis and osteomyelitis. The diagnosis of foot infection in a diabetic patient should be made primarily on clinical findings. The presence of the signs of inflammation, such as:

- Induration
- Erythema
- Edema
- Pain
- Tenderness
- Warmth, with purulent drainage
- Fever – supported by laboratory findings such as elevated erythrocyte sedimentation rate, C-reactive protein and white blood cell (WBC) counts

are the keys to diagnosis. Lipsky and Berendt advocate that the presence of pus or two or more signs of inflammation should be used as clinical evidence of infection [36]. Pain and systemic signs of infection such as chills, fever and leucocytosis – however – are often lacking in diabetic patients [29,31]. Recalcitrant hyperglycemia might be the only associated clinical finding indicating the potential severity of an underlying infection [29].Infection may be superficial, superior to the fascia, or deep, extending to fascia, muscle, tendon, bone & joints

The International Consensus on the Diabetic Foot proposed an approach for determinin the severity of infection [36]. The key elements are summarized by the acronym PEDIS (perfusion, extent/size, depth/tissue loss, infection, and sensation) (Table 1). Deep soft tissue infections can be associated with gas-producing pathogens. Gas gangrene is relatively uncommon in diabetic foot infections [37]. Differential diagnosis of gas-producing mixed soft tissue infection and gas gangrene is shown on the table, based on the work on Cunha [37](Table 2).

Beside gas gangrene the other specifically life-threatening infection is necrotizing fasciitis, for which mortality is currently approaching 30% [37]. It is characterized by rapidly spreading soft tissue necrosis, involving both the superficial and deep fascia with systemic toxicity including shock and organ failure [38] with spiking fever and pain at the site of the infection [39]. Necrotizing fasciitis can be diagnosed by recognizing the tense swollen extremity with erythema and cellulitis that does not respond to antibiotics or elevation. The patient is often toxic, and bullae and skin discoloration may be seen over the affected area.

Diagnosis of diabetic foot osteomyelitis

Patient history and physical examination are minimally helpful in diagnosing osteomyelitis. The signs and symptoms of osteomyelitis may be subtle and not different from those of an accompanying soft-tissue infection [40]. Osteomyelitis should be considered in patients with long-standing soft tissue infection, or skin ulceration, especially if it is located over a bony prominence [40]. An ulcer area greater than 2 cm^2 and deeper than 3 mm aswell as a sedimentation rate of about 40 to 70 mm/h have been shown to be predictive of osteomyelitis [41], while other blood tests, including WBC count, have not been shown to be clinically useful in diagnosing osteomyelitis [41,42].

Grayson and colleagues have shown that bone infection can be identified by probing the ulcer base with a sterile probe [43]. Contacting a bony surface with the probe has a positive predictive value of almost 90% for osteomyelitis, the sensitivity proved to be 66% and the specificity 85% of this simple clinical test [43]. The value of this test has been disputed recently [32].

Definitive diagnosis of osteomyelitis, and the identification of the etiologic agent, may require histologic examination of the bone. Bone biopsy is appropriate if the diagnosis remains doubtful, or the etiologic agents cannot be proven because of confusing culture results or previous antibiotic therapy [7]. Pathology criteria of osteomyelitis includes inflammatory cells, osteonecrosis, and marrow fibrosis.

Diagnostic imaging

Plain radiographs often show the outline of the ulceration in the soft tissue. This may be useful for determining which bony prominence is causing the overlying pressure [32]. Radiography is useful for showing the soft tissue emphysema suggestive of a gas-forming infection [32].

Plain radiograph is the initial screening method for osteomyelitis. Demineralization, periosteal reaction and bony destruction, the classic radiographic triad of osteomyelitis, appears only after 30 to 50% of the bone is destroyed, a process taking at least 2 weeks [34]. This triad may also be seen in other diabetic foot pathologies such as osteoarthropathy, fracture, joint deformities, but when the patient does not have signs of neuropathy, Charcot joint as a possibility can be ruled out [34].

Plain radiographs have a sensitivity of 28 to 93% in diagnosing osteomyelitis in patients with foot ulcers and the specificity of 25 to 92% [44]. This wide range means that a negative finding does not rule out osteomyelitis, and a positive finding alone does not confirm it: either a positive microbiological or pathological finding of bone biopsy or other imaging methods for verifying osteomyelitis is required.

Magnetic resonance imaging (MRI) is becoming the standard imaging test for soft tissue and bone infections in the foot [32]. The superior soft tissue imaging of this modality allows for the differentiation, and most importantly the localization of cellulitis, fasciitis, pyomyositis, abscess and osteomyelitis [32]. Necrotizing fasciitis is best diagnosed by MRI with gadolinium contrast. Absence of gadolinium contrast enhancement on T1-weighted images reliably indicates fascial necrosis [45].

Abnormal bone marrow signal, soft tissue mass and cortical destruction seen on MRI are strongly suggestive of osteomyelitis [34]. The demonstration of sequestrum formation, sinus tracts and associated soft tissue ulceration increases the diagnostic certainty. Charcot joint and osteomyelitis are however, often indistinguishable even by MRI [46].

Computed Tomography (CT) may show sequestra, cortical destruction, periosteal new bone formation, and small foci of gas within the bone better than MRI. However, CT cannot distinguish between pus, granulation tissue, inflammation, or fibrosis [44]. On three-phase

Table 1. Classification of a diabetic foot infection.

Clinical manifestations of infection	Infection severity	PEDIS grade
Wound lacking purulence or any manifestations of inflammation	Uninfected	1
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	2
Infection (as above) in a patient who is systemically healthy 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	3
Infection in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, severe hyperglycemia, or azotemia)	Severe	4

PEDIS: Perfusion, Extent/size, Depth/tissue loss, Infection, and Sensation
Lipsky BA, Berendt AR, Deery HG et al. Diagnosis and treatment of diabetic foot infections. Clin. Infect. Dis. *39(7), 885–910 (2004) [36].*

technetium(Tc)-phosphonate bone scintigraphy focal hyperperfusion, focal hyperemia and focal bony uptake on delayed images is highly sensitive for diagnosing osteomyelitis, but the specificity is varying from 25 to 80% [44]. The same pattern may also be seen in the case of fracture, neuropathic joint and longstanding cellulitis. Therefore a positive bone scan is not necessarily indicative of osteomyelitis, but a negative result excludes it with a high degree of probability [44].

Leukocyte-labeled scintigraphy [47] – especially combined with bone marrow imaging [44,48], and scanning with monoclonal antibodies, such as murine monoclonal antibody [34] or monoclonal antigranulocyte antibody [49] – improves specificity. In practice, plain x-ray films combined with leucocyte-labelled scintigraphy are the most commonly used methods, in most cases providing sufficient diagnostic probability.

Table 2. Differential diagnosis of gas-producing mixed soft tissue infection and gas gangrene.

Gas-producing, mixed soft-tissue infection	Gas gangrene
Large amount of gas on x-ray films	Little gas on x-ray films
Not discoloured	Discolored
Not involves muscle	Always involves muscle
May have fever	No fever
Foul smelling fluid	Sweetish smelling fluid
Many polymorphonuclears	Few polymorphonuclears
Multiple aerobic and anaerobic pathogens	Only anaerobic pathogens

Microbiology of diabetic foot infections

As nearly all ulcers are contaminated, culture of noninfected wounds is generally not recommended. When infection is suspected, culturing the causative agents is essential. Sampling requires rigorous curettage aspiration, scrubbing and/or biopsy of deeper tissues. The sample should be cultured quickly, both aerobically and anaerobically. Superficial techniques, such as swabbing the wound or obtaining purulent discharge from the wound, frequently do not correlate with deep tissue cultures or tissue/or bone aspirations [17,50,51]. Therefore it is recommended to obtain samples from deep tissues, and even from the bone, when bone is exposed [40].

Most mild, acute infections, particularly those in antibiotic-naïve patients, are usually monomicrobial, caused by aerobic Gram-positive cocci [17,52]. Between 50 and 80% of infections are caused either by coagulase-positive or -negative staphylococci [52–56]. Methicillin-resistant *Staphylococcus aureus* (MRSA) has become increasingly prevalent in diabetic foot wounds [56]. Of the staphylococcus strains, 15 to 40% are MRSA and are frequently isolated from patients who have previously received antibiotic

therapy, were treated in hospital, or at chronic care facilities [52,54,57]. MRSA colonization had an adverse effect on wound healing [54,58]. Streptococci are involved in approximately 10 to 40% of all cases [52–55], often as part of a polymicrobial infection [53,54].

Necrotizing fasciitis has classically been connected with streptococci. In the material of Reyzelman and colleagues, non-group A streptococci were the only or predominant pathogens in all of the 20 necrotizing fasciitis patients with insulin-dependent diabetes [59]; group B streptococci were isolated in 17, group G in five and both in two cases. Patients with diabetes are prone to infection with non-group A Streptococci, particularly groups B and G, [60–63] and also at particular risk for developing necrotizing fasciitis [60–62]. A review of 163 cases of necrotizing fasciitis found that 71% of those with a positive result of tissue culture had polymicrobial infections [64].

Gram-positive cocci remain the most frequently isolated organisms in the more severe infections; Gram-negative aerobic bacilli accounted for less than a third of the total microorganisms [52–55]. Gram-negative bacilli are found in many patients with chronic or previously treated infections [31]. Anaerobic species were less frequent as they often participate in a polymicrobial infection [52–55]. Obligate anaerobic species are most frequent in ischemic wounds with necrosis or those involving deep tissues [31]. Diabetic foot infections are polymicrobial in 40 to 80% over all species [17,51–54].

Prevention

Patients' education regarding foot hygiene, skin care, nail care, daily visual foot inspection, proper footwear, and appropriate foot care administered by qualified professionals may reduce injuries leading to foot ulceration and amputation [65]. Regrettably, on routine visits of diabetic patients to the primary care physician, foot examinations are performed in only 14% of cases [66], and even patients admitted for diabetic foot complications are almost never adequately evaluated [23,67]. A simple, low-cost educational intervention for physicians and medical staff significantly improved the adherence to foot examination guidelines for patients with diabetes [66]. Annual, detailed foot examination, including the assessment of protective sensation, foot structure, biomechanics, vascular status, and skin integrity, is necessary to identify high -isk conditions [68]. People with one or more high-risk conditions should be evaluated more frequently for the development of additional risk factors [68].

The following foot-related risk factors are associated with an increased risk of amputation [68]:

- Peripheral neuropathy with loss of protective sensation
- Altered biomechanics (in the presence of neuropathy)
- Evidence of increased pressure (erythema, hemorrhage under a callus)
- Bony deformity
- Peripheral vascular disease with decreased or absent pedal pulses
- A history of ulcers or amputation
- Severe nail pathology

Protective soles and shoes, the debridement of calluses, operative procedures to correct deformities reduce the risk of ulcerations and the development of infectious complications [69]. Patients with peripheral arterial disease, especially with delayed ulcer healing, may require vascular reconstruction [69].

Treatment of foot infections

For patients without limb-threatening infection, ambulatory treatment can be considered, provided that appropriate oral antibiotic agents are available and that the patient is reliable and has a supportive home environment. Careful follow-up is necessary. Patients should return for inspection of the wound every 2 to 5 days until resolution of the infection is clearly occuring [36]. Hospitalization is recommended in the case of [17,70]:

- Severe infection and toxicity (fever, high inflammatory parameters), requiring acute surgical treatment and/or parenteral antibiotics
- Deterioration of infection despite adequate conservative treatment
- Significant vascular impairment
- Metabolic derangement
- The patient being unable or unwilling to be adequately involved in wound care and offloading of the affected area.
- If the patient is unlikely to comply with antibiotic therapy
- Multiple diagnostic tests and/or several consultations are required

Offloading

Elevation of the infected foot, strict bed-rest is needed to control the inflammatory reaction. Elevation is helpful in decreasing edema in the acute phase as well.

Surgical treatment

Ulcers heal more quickly if their surface is clean and sinuses are laid open. Repeated and vigorous sharp debridement of the devitalized tissue of the wound is recommended [31,71]. The purpose of sharp (surgical) debridement is fourfold: drainage of necrotic tissue and pus, stimulation of healing of a usually chronic wound, assessment of the extent of the infection, and obtaining specimens for culture [71].

In the instance of a suspected deep-space abscess, extensive tissue necrosis, necrotizing fasciitis, or purulent drainage, prompt surgical debridement, drainage or irrigation should be performed. Tan and colleagues evaluated the charts of 112 patients with diabetic foot infection [72]. All patients were classified into two groups. Group I included patients who underwent no surgical intervention during the first 3 days of hospitalization but received intravenous antimicrobial therapy. Group II included patients who underwent surgical intervention (debridement or local limited amputation) promptly and received intravenous antimicrobial therapy. Patients who underwent early surgical intervention required a significantly lower rate of subsequent above-ankle amputation and a shorter duration of hospitalization.

The term 'minor amputation' refers to an amputation distal to the tarsometatarsal joint, whereas 'major amputation' refers to one through or proximal to the tarsometarsal joint [16]. Amputation is recommended:

- When infection progresses despite antibiotic treatment, local surgery and local wound care
- In the case of extensive gangrene and toxic conditions not responding to conservative treatment
- In the case of extensive necrosis [71]
- When pain is intolerable despite adequate analgesic medication [17]
- When the patient is not medically capable of withstanding multiple salvage operations or the long hospital recovery required. In this case, the best option may also be primary limb amputation [71].

Amputation is required more often for patients with deep soft tissue infection, than for those with osteomyelitis [17].

Management of osteomyelitis traditionally involves surgical removal of infected bone, combined with antibiotic therapy [35]. However recent studies have shown than antibiotics alone may apparently eliminate bone infections in many cases [35].

Eneroth followed 112 diabetic patients with osteomyelitis [17]. 44% of the patients were reported to heal with conservative therapy, and only 37% healed with major and 5% with minor amputation. The figures are similar in other studies [73–75].

As with other forms of nonhematogenous osteomyelitis, removal of the infected bone is the best way to ensure long-term eradication. If the infected bone can be easily resected without compromising the integrity of the foot, this is often preferable to prolonged antibiotic therapy [40]. When the infection involves a digit, especially one other than the big toe, amputation may be the most cost-effective approach [40]. However major amputation or complex surgery on an ischemic limb should be better avoided, if possible [40].

Revascularization

Ischemia is often an impediment to the healing of foot infections. Vascular reconstructive surgery of the occluded limb improves prognosis and may be required prior to debridement, foot-saving surgery, and/or partial amputation [71].

Adjunctive therapies

Larval therapy

During the Napoleonic wars it was observed that those wounds accidentally infected by maggots did not become infected and appeared to heal better [76]. In recent years, the use of sterile larvae (larvae of the green bottle fly) has been investigated with encouraging results and is becoming increasingly popular for infected and necrotic wounds [77–79]. It is thought that maggots remove dead tissues by secreting powerful enzymes that break down dead tissue into a liquid form, which is then ingested [80]. Modification of fibroblast adhesion may enhance new tissue formation [81].

Granulocyte colony-stimulating factor (G-CSF) was tried as an adjunctive treatment to standard treatment of diabetic foot infections in four prospective, randomized comparative trials with conflicting results [82]. The conventional meta-analysis of these four trials demonstrated that G-CSF therapy significantly reduced the need for amputation and vascular surgery [82].

Hyperbaric oxygen (HBO) treatment is also an adjunctive treatment of diabetic foot infections. A high concentration of oxygen under increased

atmospheric pressure produces a rise in plasma-free oxygen and increases the perfusion pressure [82]. These findings suggest the possibility of correcting perfusion-related oxygen deficits, with improved wound healing [82]. Lipsky and colleagues found only three randomized controlled trials evaluating HBO treatment of diabetic foot infections [82]. All of these trials reported favorable results, but due to the high number of variables in wound healing in diabetic foot infections, none of the studies proved to be documented sufficiently to prove unequivocally the effect of HBO treatment [82]. Certainly, additional well-designed randomized, controlled trials are needed with these adjunctive treatment modalities before introducing their routine use in the treatment of diabetic foot infections.

Antibiotic treatment of diabetic foot infections

It is widely accepted that clinically noninfected diabetic ulcers should not be treated with antibiotics [31,70]. It was also demonstrated that antibiotic treatment of ulcers with bacterial colonization, but without clinical signs of infection, did not improve healing [83]. There are also opposing views, however [84]. Those who disagree do admit that bacteria cultured from the surface of ulcers should not be eradicated, but argue that bacteria cultured from biopsy specimens of the base of the ulcer may have a causative role and should be regarded as infected. This view is supported by only one study [85].

In this study, out of the 32 patients with diabetic foot ulcers not receiving antibiotic treatment, 15 developed clinical infection, seven were admitted to hospital and three required amputation. Conversely, out of the 32 patients treated with antibiotics, no clinical infection occurred. Furthermore, in the group not receiving antibiotic treatment, the ulcers of 17 patients healed while those of 27 patients healed in the antibiotic-treated group [85].

Tentolouris and colleagues found that ulcers with MRSA colonization were resistant to treatment [54]. Staphylococci secrete polysaccharides, and form a so-called biofilm [86]. A similar biofilm may also be formed by pseudomonas and enterococci [87]. Within the biofilm, the bacteria become resistant to immunoeffectors and develop decreased susceptibility to antibiotics [86,88]. Moreover, within the biofilm the phenotype of bacteria can be changed [86]. These facts may indicate, that antibiotic treatment can be useful even in the case of bacterial colonization. The newest guidelines for treatment of diabetic foot infections indicate a brief culture-directed course of antibiotic treatment, even when the clinical signs of infection are absent, that is, when the foot [36]:

- Is ischemic
- Has abnormal coloration or a fetid odor
- Has friable granulation tissue
- Is associated with unexpected pain or tenderness
- Fails to demonstrate healing in spite of adequate treatment

Clearly, this issue requires further investigation and additional, well-designed, controlled clinical trials are necessary to elucidate whether clinically, seemingly noninfected neuropathic ulcers with positive bacterial culture of the deeper tissues, should be treated with antibiotics or not.

A number of factors should be considered when choosing an antibiotic regimen for patients with diabetic foot infections. These factors are listed excellently by Lipsky, and it would appear to be useful to check these factors prior to commencing antibiotic treatment (Table 3)[70].

It is widely accepted that initial antibiotic treatment should be empirical [31,37,70]. Empirical antibiotic treatment is based on our knowledge of the common causative microbes of mild and severe foot infections and their antibiotic susceptibility [31,70]. Gram stains of pus or removed tissue examined before starting antibiotic treatment may determine whether only Gram-positive cocci or also Gram-negative rods are present in the infected lesion [32]. The general principles of antimicrobial therapy based upon the International Consensus on Diagnosing and Treating the Infected Diabetic Foot [70] are shown in Table 4.

It is very important to notice, that the primary guide to antibiotic treatment is clinical response [32]. An adjustment of empiric therapy is necessary if clinical response is not satisfactory, or the result of culture and antibiotic susceptibility data indicates shift of antibiotic treatment [36].

Treatment of mild (PEDIS Grade 2) diabetic foot infections

Mild (PEDIS Grade 2) diabetic foot infections [36] are usually caused by Gram-positive cocci: Staphylococci and group A and B streptococci [51,53,89]. The empirical treatment for the infections caused by these bacteria are semisynthetic penicillins or first-generation cephalosporins [70]. In the case of previous antibiotic treatment, polymicrobal infection with the participation of

Table 3. Factors that may influence choices of antibiotic therapy for diabetic foot infections (specific agents, route of administration, duration of therapy).

Infection related
Clinical severity of the infection
Previous (within 2 weeks) antibiotic therapy
Bone infection (presumed or proven)
Vascular status at infected site
Organism related
Etiologic agent(s) (known or presumed)
Local antibiotic susceptibility data
Patient related
Allergies to antibiotics
Host immunological status
Patient preferences
Renal or hepatic insufficiency
Gastrointestinal absorption impairment
Drug related
Safety profile (frequency and severity)
Drug interactions potential
Frequency of dosing
Formulary availability/restrictions
Cost considerations (for drug and administration)
Approval for indication
Published efficacy data

Lipsky BA: A report from the international consensus on diagnosing and treating the infected diabetic foot. Diabetes Metab. Res. Rev. *20(1), S68–S77 (2004). Copyright John Wiley & Sons Limited. Reproduced with kind permission [70].*

Gram-negative rods and/or MRSA can be presumed. If MRSA is unlikely carbapenem or clindamycin and aminoglycosid, cephalosporins, penicillin/β-lactamase inhibitor congeners, or fluoroquinolones can be selected [70]. For patients in whom MRSA is proven or likely daptomycin with or without aztreonam, linezolid with or without aztreonam, vancomycin and ceftazidime with or without metronidazole [36] may be effective. Having received the results of cultures and susceptibility tests, we can adjust antibiotic treatment accordingly, assessing also any clinical improvement [70].

For mild infections, oral treatment is preferred. Parenteral administration is indicated, when there is allergy or resistance to oral antibiotics, or gastrointestinal intolerance contraindicates oral administration [82]. The duration of treatment is preferably 1 or 2 weeks [70,90]. Local antiseptics containing silver and iodine in various preparations may be used for treating mild infection [91]. Topical antiseptics may inhibit wound healing [31], although there is no direct evidence of this. Clearly, more well-designed, controlled *in vivo* trials are required in this field. Topical silver, sulfadiazine, neomycin, polymyxin B, metronadizole, gentamycin and mupirocin have been used, but their efficacy in diabetic foot infections has not been studied in appropriate trials [31,70,90]. A topical peptide antibiotic, pexiganan acetate, has demonstrated similar efficacy to oral ofloxazine in mildly infected foot ulcers [31,92,93].

For moderate (PEDIS Grade 3) infections trimethoprim–sulfamethoxazole, amoxicillin/clavulanate, levofloxacin, cefoxitin, ceftriaxone, ampicillin/sulbactam, linezolid (with or without aztreonam), daptomycin (with or without aztreonam), ertapenem, cefuroxime (with or without metronidazole), ticarcillin/clavulanate, piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin can be used empirically [36]. For moderate infections the route of administration can be oral, with initial parenteral administration. The duration of treatment should be between 2 to 4 weeks.

Patients with severe (PEDIS Grade 4) [36] diabetic foot infections always should be treated in hospital, at least initially. The antibiotic regimen advised by the newest consensus are the following: piperacillin/tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin and ceftazidime (with or without metronidazole) [36]. Delivery should always be carried out intravenously, at least initially, with a duration of treatment between 2 to 4 weeks. In severe infection the vigilant observation of the

Table 4. Requirements for antimicrobial therapy and therapy of osteomyelitis.

Antimicrobial therapy – general principles
• Prescribe for all clinically infected wounds immediately, but not for those that are uninfected.
• Select the narrowest spectrum of therapy possible for mild or moderate infections.
• Choose initial therapy based on the most common pathogens and known local antibiotic sensitivity data.
• Adjust (broaden or constrain) empiric therapy based on culture results and clinical responses to the initial regimen.
Therapy of osteomyelitis
• Consider surgically removing any infected and necrotic bone, if possible.
• Unless all infected bone is resected, provide antibiotic treatment (with parenteral therapy, at least initially) for at least 4 weeks.
• Treating for several months with highly bioavailable oral agents (especially fluoroquinolones) without surgical resection may be effective in selected patients.

Lipsky BA. A report from the international consensus on diagnosing and treating the infected diabetic foot. Diabetes Metab. Res. Rev. *20(1), S68–S77 (2004). Copyright John Wiley & Sons. Reproduced with kind permission [70].*

clinical course is very important [32]. In the case of no improvement or worsening, an alternation in antibiotic treatment is indicated, even when the treatment covers all bacteria recovered by cultivation [82]. When culture results and antibiotic susceptibility are available these should be considered in addition to the clinical response to empiric treatment [82]. When the infection is caused by aerobic Gram-positive cocci with expected susceptibility and the patient is improving, the initially broader spectrum treatment can be reduced to a semisynthetic penicillin or first-generation cephalosporin [82].

Antibiotic treatment of osteomyelitis of the diabetic foot

The choice of antimicrobial agent for osteomyelitis should be based on bone culture. If culture is not appropriate, empirical treatment should be started with one of the regimens advised for severe infection. Coagulase-negative *S. epidermidis* is a frequent etiologic factor, but we know that 60% of this agent is methicillin-resistant [40,94]. If empirical treatment is needed, *S. aureus* should be always covered [40]. Neither quinolons, nor rifampicin should be used as monotherapy, although combination therapy of them is acceptable [95].

Surgical removal of infected and necrotic bone should always be considered, although it was shown that osteomyelitis can be arrested, even cured, with antibiotic treatment alone in two-thirds of cases [96,75]. In this case, antibiotics should be administered parenterally for at least for 4 weeks, and then orally for 2 to 6 months [70]. If all the infected bone can be removed, the duration of antibiotic treatment can be cut much shorter, lasting only 2 to 4 weeks. Antibiotic-impregnated beads, or orthopedic implants, can be used locally [97,98]. Gentamycin-impregnated beads should be avoided as they induce antibiotic-resistant, small colony variant staphylococci [31,95]. The outcome of osteomyelitis of the foot in diabetics improved considerably in the last two decades. Inspite of this, in a recent study, 75% of infectious disease consultants were of the opinion that a failure rate of 7.8% regarding diabetic patients foot osteomyelitis is acceptable, while for the remaining 25%, a 28.4% failure rate was even considered acceptable [99]. There is certainly room for further improvement.

Evidence-based antibiotic treatment

Prospective, randomized controlled clinical trials of antibiotic treatments for diabetic foot infections are not numerous due to the difficulties designing these trial types in this field – it is difficult to collect homogeneous patient material and a placebo arm of these trials should certainly be avoided. Even double-blind studies often cannot be organized. The most important prospective controlled trials are shown on Table 5. In most of the randomized, controlled trials listed in this table, the different antibiotic regimens in both arms were equally effective. In some trials, only one section contained diabetic patients and the other had non-diabetic foot infections. For other trials, only second-hand information was available as the results have been reported in different meetings or congress abstracts [36]. Clearly more prospective, randomized, controlled trials should be carried out on more homogenous patient materials, with or without osteomyelitis, and with the same grade of infection.

Expert opinion

The incidence of diabetic foot infections is still very high: 15% of diabetic patients develop foot ulcers during their lifetime [100], and more than 50% of ulcers become infected [4]. Between 7 and 15% of patients with diabetic foot ulcers develop osteomyelitis [6,8]. The infections are often limb- or life-threatening. Diabetes related foot ulceration and infection is the cause of nearly half of the nontraumatic LEAs [9,10]. One of the major goals of the European St Vincent Declaration on Diabetes is to reduce amputations by 50% by the year 2010 [22]. This goal can only be achieved through more effective

Table 5. Antibiotics showing clinical effectiveness in prospective controlled trials of diabetic foot infections.

For oral route	Refs
Cephalexine	[53]
Amoxicillin/clavulanate	[101,102]
Ciprofloxacin	[103]
Levofloxacin	[104]
Oflaxacin	[101]
Clindamycin	[53]
Linezolid	[102]
For parenteral route	
Cefoxitim	[105]
Ceftizoxime	[105]
Ampicillin/sulbactam	[36,101,102,106]
Imipenem/cilastatine	[106]
Piperacillin/tazobactam	[107]
Ertapenem	[104]
Ciprofloxacin	[103]
Clinafloxacin	[107]
Oflaxacin	[101]
Linezolid	[102]
Ertapenem	[36]
Daptomycin	[36]
Ticarcillin–clavulanate	[104]

prevention and treatment of diabetic ulcers, as ulcers are the most common gateways to infection. Prevention of foot ulcers can be best achieved by good glycemic control, patients education, regular assessment of feet of diabetic patients and avoiding the development of high pressure areas within the foot. This latter can be achieved by using proper footwear, inlays and soles [69].

The effective local and general treatment of noninfected and/or infected ulcers may dramatically reduce the incidence of lower leg amputations [12,16]. Noninfected ulcers can be treated by regular and effective wound care and reconstructive vascular surgery [29], and also, but rarely, growth-factors, HBO and moulded casts for example, can be used for this purpose [31,82].

The diagnosis of foot infection is primarily based on physical signs, like redness, other inflammatory signs, pus formation [82]. Non infected only colonized wounds should not be treated with antibiotics [36]. There is a debate, however, whether bacteria cultured from deep layers of the wound should or should not be regarded as causative agents [84]. Clearly, more research is needed in this field.

Mild and moderate, but also severe foot infections, are usually monobacterial, caused by Gram-positive bacteria, first of all by staphylococci and streptococci [70]. Polymicrobal infections are usually present if the patient was treated previously with antibiotics [31]. MRSA infections usually occur in hospitalized patients [54]. Anaerobe infection is normally rare [52]. Cultures should be taken from the deep structures of the wound, preferably from a biopsy specimen. and superficial swabs are not satisfactory [50]. Mild and moderate infections can be treated providing suitable wound care and 1 or 2 weeks of antibiotic treatment covering Gram positive cocci, if the patient was not treated previously by antibiotics or the patient was not hospitalized previously, is maintained [36].

Patients with severe infections having constitutional symptoms and signs such as fever, should be hospitalized. Hospitalization is necessary for non-complicated patients when ambulatory treatment is not successful or surgery, parenteral antibiotic treatment is planned [70]. Although antibiotic treatment should be initially based on culture and susceptibility data, treatment should be started on an empiric basis. Even in the case of severe soft tissue infections, the duration of antibiotic treatment is usually no longer than 2 to 4 weeks [70]. Diabetic foot osteomyelitis is usually contiguous, spreading from the soft tissue to the bone [40,35]. The diagnosis of osteomyelitis is also based on clinical and x-ray findings. However, labelled leukocyte scan and MRI can also be used [34,44]. Antibiotic therapy of osteomyelitis should be based on bone cultures [40,35]. Although osteomyelitis can, in some cases, also be healed with long term antibiotic treatment [35,40], beginning via the intravenous route for 3 to 4 weeks, in many cases. surgical removal of the infected bone part is necessary and this considerably shortens the healing time [70]. Unfortunately there are very few prospective randomized controlled trials of the antibiotic treatment of diabetic foot infections [36]. Clearly, further trials on more homogenous patient groups are necessary.

Outlook

Both the incidence and prevalence of diabetes is increasing, and therefore an increase in the number of diabetic foot infections can be expected. Both the medical profession, and the lay society should be made fully aware of the severity of diabetic foot infections, and their

Executive summary

- Diabetic foot infections are very common and are often limb- or life-threatening.
- Predisposing factors are: metabolic derangements, foot deformities, unsatisfactory personal foot hygiene and foot care, diabetic neuro- and vasculopathy and foot ulcers.
- Patient education and regular assessment of the foot of the diabetic patient is mandatory for preventing foot infections.
- Team including endocrinologist, podiatrist, infectious diseases specialist, vascular surgeon and non-medical personnel with experience on this field is required for effective treatment.
- Effective local treatment of noninfected foot ulcers may prevent infections.
- Ulcers with bacterial colonization, but without clinical signs of infections should not be treated with antibiotics, unless there is a methicillin-resistant *Staphylococcus aureus* colonization, the ulcer is painful and/or tender, or does not heal as expected despite appropriate treatment.
- For bacterial culture no superficial swabs, but swabs of debrided base of the ulcer or biopsy specimen of the infected tissue should be sent if possible.
- Early diagnosis of infection assessing its severity, and weighing the probability of causative agents is very important.
- Empirical antibiotic treatment should be started immediately according to the severity of the infection and the suspected causative agents.
- The result of treatment should be regularly assessed, especially in limb or life threatening cases, and shift in treatment – including surgical interventions – should be decided, if necessary.
- Diabetic foot osteomyelitis is usually contiguous of origin. In the case of deep infected wounds osteomyelitis should be suspected.
- Osteomyelitis should be treated based on bone culture if possible.
- Duration of antibiotic treatment of soft tissue disorders should be 1 to 4 weeks, of osteomyelitis 1 to 6 months, when surgical removal of the infected bone was not performed. When the infected bone was removed 2 to 4 weeks of antibiotic treatment should be satisfactory.

knowledge about its prevention should be more detailed. Diabetic patients and their families should be educated about proper foot-care, early signs of neuropathy, ulceration and infections. In addition, doctors – especially general practitioners – and nurses should be trained on how best to educate patients and regularly assess the feet of their diabetic patients, aswell as how to treat the diabetic foot with or without infections. Teams should be formed consisting of endocrinologists, general practitioners, vascular surgeons, infectious disease specialists, physiotherapists, dieticians and nurses both in hospitals and outpatient clinics for comprehensive treatment of diabetics with foot disease. More research should be done about the more effective prevention and treatment of diabetic neuropathy, and neurovascular foot ulcers. More research should be done about the microbiology of non-infected and infected foot ulcers, osteomyelitis, etc. The pathogenic role of biofilms-formed of bacterial glycoproteins, host tissue and bacteria – should be further studied.

It should be studied further, whether clinically non-infected only colonized foot ulcers should be treated with antibiotics, especially when the colonizing bacterium is MRSA, or the ulcer is not properly healing. More multicentre RCT-s are required about the antibiotic and adjuvant treatments of diabetic foot infections including osteomyelitis. The guidelines for treating diabetic foot infections should be field tested.

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