

Diabetic foot infections: state-of-the-art

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Foot infections are frequent and potentially devastating complications of diabetes. Unchecked, infection can progress contiguously to involve the deeper soft tissues and ultimately the bone. Foot ulcers in people with diabetes are most often the consequence of one or more of the following: peripheral sensory neuropathy, motor neuropathy and gait disorders, peripheral arterial insufficiency or immunological impairments. Infection develops in over half of foot ulcers and is the factor that most often leads to lower extremity amputation. These amputations are associated with substantial morbidity, reduced quality of life and major financial costs. Most infections can be successfully treated with optimal wound care, antibiotic therapy and surgical procedures. Employing evidence-based guidelines, multidisciplinary teams and institution-specific clinical pathways provides the best approach to guide clinicians through this multifaceted problem. All clinicians regularly seeing people with diabetes should have an understanding of how to prevent, diagnose and treat foot infections, which requires familiarity with the pathophysiology of the problem and the literature supporting currently recommended care.

Keywords: diabetes complications, diabetes mellitus, foot complications, infections

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Introduction

Diabetic foot infections (DFIs) are defined as a clinical syndrome characterized by local findings of inflammation or purulence (sometimes accompanied by systemic manifestations of sepsis) occurring in a site below the malleoli in a person with diabetes. Estimates of the incidence DFIs range from a lifetime risk of 4% in all persons with diabetes to 7% yearly in patients treated in a diabetic foot centre [1]. Most DFIs occur in a neuropathic or neuroischaemic ulcer, which serves as a point of entry for pathogens. With the exception of erysipelas and posttraumatic (including postsurgical) infection [2], DFIs are almost always epiphenomena, i.e. the consequence of progressive peripheral polyneuropathy, with associated loss of protective sensation coupled with gait disorders, anterior displacement of weight-bearing during walking [3] with reduced mobility, and arterial insufficiency in a mostly elderly patient population [4]. Vascular disease, mostly in the form of occlusive atherosclerotic disease of the arteries below the knee, sometimes accompanied by small vessel dysfunction [5], can cause ischaemic ulcers and may contribute to elevated plantar pressures and to prolonged duration of foot-to-floor contact [6]. Figure 1 shows the major steps in the pathophysiological 'chain' ultimately leading to DFI [7], and the role of different healthcare workers who may help reverse or postpone the progression of infection and lower extremity amputation.

Developing a DFI is often the pivotal event leading to lower extremity amputation. Diabetes is the leading cause of non-traumatic lower extremity amputation worldwide. Diabetes-related amputations at various levels (from toe to above-knee) are responsible for about 60% of all amputations in developed countries [8] and confer a high burden of financial cost, morbidity and mortality. In high-income countries, treatment costs (published in 2000) for a DFI range between US \$30 000 without amputation and US \$58 000 with amputation [9]. Diabetes is also associated with a significantly higher rate of postoperative stump dehiscence compared to amputations for purely ischaemic reasons [10]. The presence of osteomyelitis further raises the costs for hospitalization because of the need for additional diagnostic studies, prolonged medical treatment and surgeries; specifically, the use of antibiotics is at least doubled [11]. When amputation is needed, a high level (i.e. transtibial) procedure is more often indicated because of irreversible ischaemia than because of uncontrolled infection [12]. Most amputations, however, reflect the multimodal foot problems related to diabetes, emphasizing the need for a multidisciplinary approach (figure 1) [7]. All clinicians regularly seeing persons with diabetes should have an understanding of how to prevent, diagnose and treat DFIs. Because of the burgeoning research in this area, this review aims to help these clinicians be aware of the developments in this field of science.

Literature Search Methodology

Several systematic reviews of the literature have been conducted in recent years [13]. To update and expand

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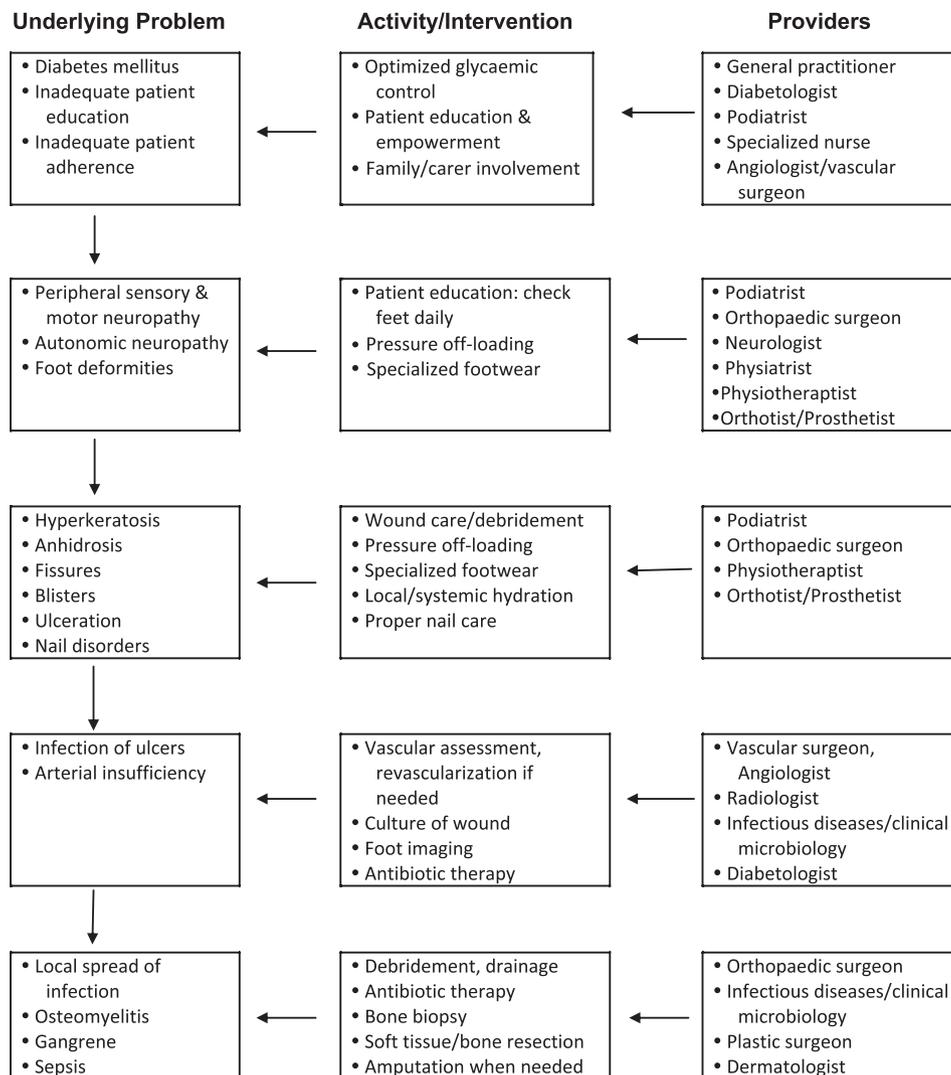


Figure 1. Overview of causes and management of diabetic foot complications.

on these, we conducted a non-systematic literature search through June 2013 using the PubMed database with the MeSH terms ‘diabetic’, ‘foot’ and ‘infection’ in English and French languages. We concentrated on *in vivo* human data published within the last 10 years, and excluded basic experimental publications, studies performed in animals, papers lacking original human clinical data (other than guidelines), those highlighting only surgical techniques or radiological diagnoses and those with non-clinical data. We selected papers initially by reading their abstracts, then obtaining the full contents of relevant sources. We also reviewed the references of retrieved articles seeking any additional references. In this review, we will concentrate on the epidemiology and medical treatment of DFIs, rather than their pathophysiology.

Risk Factors for Infection

Few studies have specifically assessed factors associated with the occurrence of a DFI. One prospective, multicenter study

compared 150 diabetic patients with DFI with 97 who did not develop infection [14]. Factors significantly associated with DFI were bone contact on probing; foot ulcer duration of longer than 30 days; a history of recurrent foot ulcers; traumatic aetiology of the ulcer; and, peripheral vascular disease. Another retrospective review of 112 patients with a severe DFI found that risk factors for infection were previous amputation, peripheral vascular disease and neuropathy [15]. Other studies have identified walking barefoot as a risk for infection. Of note, these risk variables are similarly associated with recurrence of ulcers [16] or reinfection after successful treatment.

Definition and Classification of Infection

Multiple classification schemes have been promulgated for diabetic foot complications, for most of which the infection information is a subsection of broader ulcer classifications. In contrast, the Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot

(IWGDF) developed guidelines specifically aimed to define and classify DFI, and thereby guide the therapy. The IWGDF-PEDIS-classification (an acronym standing for **p**erfusion, **e**xtent [size], **d**epth, **i**nfection and **s**ensation/neuropathy) suggests a semi-quantitative 4-point scale to describe infection that can be used for including patients in research studies, but also appears to help predict the outcome of a DFI [17].

Because all open wounds will be colonized with microorganisms, occasionally even virulent bacteria, culture results alone cannot define infection. Some favour using quantitative microbiology (e.g. the presence of $\geq 10^5$ colony forming units/gram of tissue) to differentiate colonization from infection, but no data support this criterion in the diabetic foot and very few clinical microbiology laboratories offer this procedure. Thus, most authorities suggest that DFI be diagnosed based on clinical findings, i.e. the classical signs and symptoms of inflammation: redness, warmth, induration, pain or tenderness and purulence. Unfortunately, these findings are somewhat subjective. For example, foot ischaemia, gout, pyoderma gangrenosum [18] or Charcot neuro-osteoarthropathy may mimic the inflammation of infection. Furthermore, pain may be mitigated by (or attributed to) peripheral neuropathy, and ischaemia may limit erythema, warmth and induration. Therefore, some wound-healing authorities suggest using 'secondary' findings to diagnose infection, such as wound friability, undermining or poor granulation tissue, foul odour or unexpectedly slow healing. Systemic inflammatory signs (such as fever, chills, hypotension, delirium), elevated serological inflammatory markers (such as leukocytosis, elevated sedimentation rate, C-reactive protein or procalcitonin levels) [19] or positive blood cultures define serious infections, but are infrequent in DFI.

The results of microbiological tests, such as a Gram-stained smear or culture from diabetic foot wound specimens, must be interpreted with reference to the clinical situation. There is no evidence that treating a clinically uninfected wound with antimicrobials has any value in either preventing infection or improving ulcer healing. When there are clinical signs of infection, however, obtaining an appropriate sample for culture and sensitivity testing helps guide antibiotic therapy. Specimens should be taken after cleansing and debriding the wound from deep, non-necrotic tissue or pus, to lessen the chance of isolating colonizing species. Superficial cultures obtained with cotton swabs are easily collected, but are less reliable than tissue biopsies and should be avoided. Most studies have found that swab specimens have more isolates (likely contaminating or colonizing flora) than aseptically obtained deep tissue specimens and also may miss true pathogens, especially anaerobic or fastidious species. In particular, most studies with diabetic foot osteomyelitis have found that neither superficial nor deep soft tissue cultures correlate well with those of bone specimens [20]. One study suggested, however, that repeated bone surface swabbing yields similar results compared with bone culture in patients with a wound with underlying clinical osteomyelitis [21], but this needs to be confirmed in larger trials.

Diagnosis of Osteomyelitis

Infection of bone underlying a diabetic foot ulcer should be suspected in the presence of a large or deep wound, especially

if it is chronic and overlying bone, or if a toe is red and swollen. Most blood tests are of limited value in diagnosing osteomyelitis, but an erythrocyte sedimentation rate of over 70 is highly suggestive. Of note is that one study found that a physician's clinical judgment about the presence of osteomyelitis had a positive likelihood ratio of 5.5 and a negative likelihood ratio of 0.54 [22]. The probe-to-bone test, in which a hard gritty structure is palpated with a sterile, blunt metal probe, is both easy to perform and useful. A negative probe-to-bone test in a patient in whom the pretest probability of osteomyelitis is low is reassuring [23], but does not rule out osteomyelitis [24]. On the other hand, a positive test in a patient in whom clinical suspicion is high (especially if the plain X-ray is suggestive of osteomyelitis) has a high predictive value for bone infection [25].

The gold standard for diagnosing osteomyelitis remains the combination of microbiological culture and histopathological examination of bone [26]. Bone specimens may be obtained at surgery or by transcutaneous biopsy. Although needle puncture of deep soft tissue near bone does not reliably predict the results of bone cultures [27], puncture of the bone itself may be an easy way to obtain bone culture at the bedside [28]. The first test to consider when osteomyelitis is suspected is plain radiography, but early infection may be missed because it takes several weeks for the findings of bone infection to be detected. Characteristic features of osteomyelitis on plain X-rays include periosteal elevation and erosions of the osseous borders, but interobserver reproducibility of detecting these signs is poor, especially among inexperienced observers [29]. The reported sensitivity of plain radiography in diagnosing osteomyelitis ranges from 28 to 75%, with one review citing a pooled sensitivity among four studies of 0.54 and specificity 0.68 [22]. Repeating and comparing foot X-rays over time is more likely to detect osteomyelitis than a single series.

In some patients, advanced imaging is needed to detect osteomyelitis. In these situations, magnetic resonance imaging (MRI) is considered the best available technique, not only for diagnosing osteomyelitis but also for better visualizing deep soft tissue infection or sinus tracts. One meta-analysis, reported a pooled sensitivity of 0.90, and the diagnostic odds ratio was 24.4 [30]. In another meta-analysis the pooled sensitivity was 77–100%, but the specificity was only 40% [31]. Undoubtedly, the value of this (like most tests) varies with the skill and experience of the interpreting radiologist, and MRI does not need to be routinely obtained [32]. Computed tomography (CT) scans, more readily available in some centres, are usually less expensive and may be useful when MRI is contraindicated. Nuclear medicine scintigraphic examinations are certainly more sensitive than plain X-rays for detecting osteomyelitis, but bone scans have a low specificity. If scintigraphy is needed, leukocyte scans are superior to bone scans, but we think these tests should usually be reserved for long-bone osteomyelitis or prosthetic joint infections. Newer procedures, such as SPECT-CT, PET/CT or PET/MRI, show promise and may be even more accurate than MRI, but to date there have been only a limited number of studies in DFI. Of note, in patients undergoing percutaneous bone biopsy for suspicion of osteomyelitis who have a negative culture, one of four will develop osteomyelitis in the next 2 years [33].

Microbiology of DFIs Around the World

In Western developed countries, mild community-acquired infections in patients who have not recently been treated with antibiotics are mainly caused by aerobic Gram-positive cocci, especially *Staphylococcus aureus* and, to a lesser degree, by β -streptococci (usually group B) or coagulase-negative staphylococci. One study using molecular microbiological methods found that ulcer depth is directly correlated with the presence of *S. aureus* [34]. In chronic wounds, especially those in a patient who has been treated with antibiotics, infections are more often polymicrobial, including aerobic Gram-negative and obligate anaerobic bacteria. Recently, epidemiological surveys from subtropical, less-developed countries have reported that *S. aureus* is less prevalent than noted in developed countries (30% vs. 75%) while there is a considerably higher prevalence of Gram-negative rods, especially *Pseudomonas aeruginosa* (Table 1). The reasons for this geographical difference has not been elucidated, but may be related to differences in specimen types, laboratory techniques, prior antibiotic use, availability of non-prescription (over-the-counter) antibiotic agents, foot sweating and washing or reporting bias. Of note, most of these reports emanate from countries in arid and hot areas, especially India [35]. It might also be that the microbiology of DFIs is evolving slowly towards more Gram-negative microorganisms [35] in some regions, whereas in other regions of the same country infections with *S. aureus* may still be dominant [36]. Areas of the southwest of the USA have also reported a relatively low proportion of DFIs caused by *S. aureus* [37] and isolation of *P. aeruginosa* is more frequent in nosocomial DFIs [38].

Traumatic wound infections [39,40] and cultures of deep wounds with moderate to severe infections, especially in previously antibiotic-treated patients, are usually polymicrobial with mixed Gram-positive cocci (*vide supra*), Gram-negative rods (e.g. *Escherichia coli*, *Proteus*, *Klebsiella*), sometimes including non-fermentative Gram-negatives (*P. aeruginosa*), and anaerobes (e.g. *Finnegoldia*, *Bacteroides*) (Table 1). Severe infections may harbour *P. aeruginosa*, especially in cases of deep puncture wounds and in patients whose feet are frequently exposed to water. Fungi are rarely principal pathogens and are thus mostly highlighted in case reports [41]. When looked for carefully by clinical laboratories, fungi have been regularly cultivated, as have anaerobes [41–44], but the clinical importance of these findings is unclear. Parasitic or mycobacterial DFIs have rarely been noted in published reports.

A recent problem has been the isolation of multidrug resistant organisms (MDROs) from DFIs. The predominant resistant pathogen has been methicillin-resistant *S. aureus* (MRSA). After many reports of this pathogen in DFIs from the mid-1990s to the early 2000s, more recent studies suggest the prevalence may be decreasing in most countries. Lately, the antibiotic resistance problem of greatest concern has been Gram-negative organisms that produce extended-spectrum β -lactamases (ESBLs) or carbapenemases. Overall, the likelihood of isolating MDROs from a DFI has increased over the past decade [42,45,46].

Treatment

Orthopaedic Surgery, Podiatry and Revascularization

Most DFIs require both medical and surgical interventions. Surgery is particularly important for dealing with abscesses, necrotizing fasciitis and a substantial proportion of osteomyelitis cases (e.g. when there is necrotic bone [47]). Many DFIs will require debridement or incision and drainage, and some patients will benefit from revascularization or procedures to correct anatomic problems or gait disorders. Details regarding the surgical approach to DFIs are important, but beyond the scope of this review.

Podiatric care is especially aimed at debridement of callus and necrotic tissue, treatment of blisters, caring for nails and selecting proper footwear. Repeated removal of calluses is especially important, as emphasized by the fact that their presence may cause 18 tons of excess plantar pressure each day [48]. Surgical treatment for DFI without concomitant antimicrobial therapy is possible [49], but the available reports from the pre-antibiotic era demonstrate high mortality rates, despite the fact that most patients underwent major (often above the knee) amputations. While urgent surgery is needed for most deep severe infections, some orthopaedic or vascular procedures may best be delayed until infection is better controlled. Some procedures, such as the correction of foot deformities, arthrodesis [50] or combination of correction and debridement for infection [51], may also serve to prevent DFIs. For example, flexor tenotomy, a surgical intervention with a low surgical site infection rate [52], may be highly efficacious (>90% success within 5–8 weeks) for prevention and healing of distal toe ulcers [52,53].

All patients with a diabetic foot wound require a vascular assessment. Those with clinically compromising arterial insufficiency of the foot require revascularization, if feasible. This may be done by either endovascular or open methods [54]. Contrary to what some profess, infrapopliteal endovascular revascularization, even in patients with long-standing diabetes, is possible with modern techniques, at least in resource-rich settings [55,56].

Antimicrobial Therapy

Antibiotic therapy is almost always necessary, but often not sufficient, to cure DFIs. It must usually be combined with one or more surgical procedures, pressure off-loading and proper wound care. Initial antibiotic therapy for most patients must be selected empirically, and should be based on the presenting clinical features, knowledge of the local antibiotic resistance patterns and an assessment of infection severity. Several principles may help to avoid selecting either an unnecessarily broad or an inappropriately narrow regimen [57]. Antibiotic coverage should always include *S. aureus*, the commonest pathogen in most situations. If the prevalence of methicillin-resistance among *S. aureus* isolates is known to be high, or if the infection is more than mild, anti-MRSA therapy is advisable. Therapy should be broadened to target Gram-negative pathogens in all severe and many moderate infections, or if the patient has failed to respond to prior narrower-spectrum antibiotic therapy. In these latter cases, it is especially important

Table 1. Results of selected reports from around the world over the past decade of the microbiology of diabetic foot wounds.

First author [Reference]	Country	Year	Types of wounds	No. of patients	Percentage of isolates from wound culture					
					Staphylococci	Streptococci	Gram- positive	Gram- negative	<i>Ps. aeruginosa</i>	Anaerobes
Carvalho [109]	Brazil	2003	Infections	141	20	4	29	59	7	12
Candel [110]	Spain	2003	Infections	27	49	15	78	22	1	2
Anandi [111]	India	2004	Infections	107	14	—	—	—	—	4
Unachukwu [112]	Nigeria	2005	Gangrene	60	56	—	—	—	—	—
Senneville [113]	France	2005	Bone	76	52	12	—	18	2	5
Abdulrazak [114]	Kuwait	2005	Infections	86	38	17	74	26	18	11
Shankar [115]	India	2005	Infections	77	—	3	42	58	30	6
Yoga [116]	Malaysia	2006	Infections	44	20	—	—	—	14	—
Gadepalli [72]	India	2006	Ulcers	80	20	0	33	51	10	15
Sharma [117]	Nepal	2006	Ulcers	—	38	—	—	—	18	—
Örmen [118]	Turkey	2007	Bone	50	—	—	40	60	—	—
Raja [119]	Malaysia	2007	Infections	194	44	25	45	52	25	—
Çetin [120]	Turkey	2007	Infections	65	18	6	59	41	8	3
Dowd [121]	USA	2008	Ulcers	40	8	37	—	—	15	18
Umadevi [122]	India	2008	Infections	105	17	0	29	71	17	0
Khoharo [123]	Pakistan	2009	Infections	60	20	3	27	73	48	2
Ramakant [35]	India	2010	Ulcers	447	19	3	31	57	17	1
Zubair [124]	India	2010	Infections	60	31	0	38	62	11	0
Özer [43]	Turkey	2010	Infections	78	17	7	38	56	19	—
Mendes [125]	Portugal	2011	Infections	49	84	4	85	19	1	14
Hayat [126]	Pakistan	2011	Infections	85	18	5	27	68	27	2
Pappu [127]	India	2011	Infections	104	21	4	—	>67	23	0
Malone [128]	Saudi-Arabia	2011	Toe bone	34	33	9	57	29	9	0
Aziz [129]	Singapore	2011	Infections	100	40	21	—	—	26	30
Dezfulian [138]	Iran	2011	Infections	69	43	5	55	45	6	5
Aamir [36]	Pakistan	2011	Wounds	114	55	5	—	—	4	—
Tiwari [130]	India	2012	Infections	62	—	—	32	68	—	—
Swarna [131]	India	2012	Infections	62	30	0	44	56	20	0
Pai [38]	India	2012	Infections	55	7	—	24	65	2	—
Widatella [47]	Sudan	2012	Bone	330	33	—	—	—	32	—
Parvez [132]	India	2012	Bone	60	9	0	14	70	7	16
Banashankari [133]	India	2012	Infections	202	19	—	32	66	13	—
Al Benwan [134]	Kuwait	2012	Infections	440	20	—	32	51	17	15
Shanmugam [135]	India	2013	Infections	50	13	—	35	65	16	—
Anjali [136]	India	2013	Infections	100	—	—	42	58	19	—
Osariemen [137]	Nigeria	2013	Infections	150	38	0	38	62	8	0
Djahmi [45]	Algeria	2013	Infections	128	43	1	45	55	8	0

Percentage values do not sum up to 100% because of mixed infections and reporting of only selected isolates.

to obtain optimal specimens for culture and to initiate an empiric regimen different from the failing one. Adding agents that are specifically active against obligate anaerobes is usually needed only if the wound is gangrenous or if there is a foetid odour. Finally, most severe infections require initial parenteral, broad-spectrum therapy [57]. Table 2 displays suggested antibiotic regimens (most often used at Geneva University Hospitals), based on the recent IDSA guidelines [13].

Using the results of appropriately obtained specimens for culture allows more targeted therapy, which usually can be narrower in scope than the empiric regimen. When cultures yield multiple organisms deciding which isolates need to be covered depends on the quality of the specimen sent for culture and the specific organisms isolated. If the specimen was aseptically obtained deep soft tissue or bone, covering all isolates may be prudent. In most situations, however, it

may be sufficient to treat just the likeliest pathogens, such as *S. aureus*, streptococci and any *Enterobacteriaceae* present in large numbers. Skin commensals, such as coagulase-negative staphylococci, corynebacteria or *Bacillus* spp., in the absence of an infection involving osteosynthetic material or hardware [59,60] can usually be dismissed. Similarly, the mere presence of skin colonization with healthcare-associated MRSA does not oblige the clinician to empirically cover this organism [58], even in the presence of underlying osteosynthetic material [61].

Because most DFIs occur in the setting of some degree of peripheral arterial disease, some have raised concerns about how well various antibiotic agents penetrate, especially in the presence of bone infection. Several studies have shown that at standard doses most β -lactam antibiotics achieve relatively low (albeit likely therapeutic) tissue levels, but clindamycin, fluoroquinolones, linezolid, rifampin, and to some degree,

Table 2. Antibiotic recommendations for empirical treatment of diabetic foot infections (adapted from Ref [13])

Severity of infection	Expected pathogens	Potential antibiotic agents	Administration route	Duration of treatment
Mild	<i>Staphylococcus aureus</i> * Streptococci	Cephalosporins, clindamycin, co-amoxiclav	Oral	1–2 weeks
Moderate	Similar to those for mild infections, plus <i>Enterobacteriaceae</i>	Co-amoxiclav, combination of quinolone + clindamycin	Oral or parenteral (to start)	2–3 weeks
Severe	All pathogens, maybe anaerobes and <i>Pseudomonas aeruginosa</i>	Piperacillin-tazobactam, cefepime, carbapenem	Parenteral, with oral switch when stable	2–3 weeks
Recent Rx with antibiotics	Consider covering <i>Ps. aeruginosa</i> , MRSA	Piperacillin-tazobactam, cefepime, carbapenem	Parenteral	2–3 weeks
Bacteremic†	Most often <i>S. aureus</i> but others possible	Based on culture and sensitivity results	Parenteral	2–3 weeks
Osteomyelitis‡	<i>S. aureus</i> , streptococci, <i>Enterobacteriaceae</i>	Based on bone culture, if possible	Oral (perhaps after initial parenteral)	4–6 weeks (if not surgically resected)

No evidence supports superiority of parenteral route over oral administration except for patients who are bacteremic or for whom antimicrobials only appropriate antibiotics are in parenteral form. Exclusion of abscesses, either clinically or radiologically (ultrasound).

*Skin colonization due to healthcare-associated methicillin-resistant *S. aureus* (MRSA) does not always require anti-MRSA coverage [58].

†Perform blood cultures if signs or symptoms of sepsis (systemic inflammatory response syndrome).

‡Avoid empirically selected therapy, if possible. Ideal antibiotic-free time before bone sampling for culture is probably 10–14 days.

tetracyclines and co-trimoxazole, have shown good oral bioavailability coupled with good penetration in bone, synovia, biofilm and necrotic tissue [59,62]. Practically speaking, however, oral absorption of almost all currently used antibiotics is usually sufficient for effective oral therapy, even in patients with vascular insufficiency. Several randomized trials in DFI have shown no superiority for any particular antibiotic agent or route of administration [63–65]. A systematic review of antimicrobial treatments for DFI concluded that the evidence was too weak to recommend any particular antimicrobial agent [66]. A critical review of randomized controlled trials on the antibiotic treatment of DFI [67] noted that discrepancies in study design, inclusion criteria, statistical methodology and definitions of both clinical and microbiological endpoints made it difficult to compare the studies or to determine which regimen may be the most appropriate. The IWGDF systematically reviewed publications through 2010 on the management of DFI [68]. Among 7517 articles reviewed, only 12 studies met the criteria for comparing different antibiotic regimens for soft-tissue infection, none of which demonstrated superiority. Similarly, there are no published data demonstrating the superiority of any particular route of delivery or duration of antibiotic therapy, either in soft-tissue infection or osteomyelitis [69,70].

Studies examining whether outcomes of DFIs caused by multiresistant pathogens are worse than for other organisms have produced conflicting data. Some have reported that patients with MDROs did not have worse outcomes [46,71], while others found that infections with MRSA were associated with poorer outcomes [72]. A potential confounder in these studies is that patients colonized with MRSA may have more often had previous unsuccessful antibiotic treatment. In light of the growing problem of antibiotic resistance, there is active research addressing various types of non-antibiotic treatment for DFIs. Among these, photodynamic inactivation [73], topical antimicrobial peptides [74] and bacteriophages [75] appear to show promise.

Only a few studies on newer antimicrobial agents for DFIs have been reported since the comprehensive systematic review of literature through August 2010 that was published in 2012 [68]. Among systemic antibiotics, a retrospectively evaluated subset of patients in a randomized controlled trial published in 2013 found that intravenous and/or oral moxifloxacin, compared with intravenous piperacillin/tazobactam followed by oral amoxicillin/clavulanate, gave similar rates of clinical cure, bacteriological eradication and adverse events [76]. In one new study of topical antimicrobial therapy recently published, a superoxidized solution applied to wounds of 14 patients who had undergone limited surgery for diabetic foot osteomyelitis was associated with healing in all [77]. Several new systemic antibiotics, including some with novel mechanisms of action, are currently under investigation for treating DFIs.

Osteomyelitis

Osteomyelitis in the diabetic foot is almost always established by contiguous spread of infection from a chronic ulcer. It occurs in up to 15% of patients with a diabetic foot ulcer [78] and about 20% of all DFIs (and over half of severe infections) involve bone at presentation [22]. The most common causative pathogen is *S. aureus*, either alone, or in a polymicrobial infection. Because the pathogenesis of bone infection is by extension from an ulcer that often has polymicrobial infection or colonization, predicting the causative pathogen(s) can be difficult. Since osteomyelitis usually requires a long duration of antibiotic treatment, often with initial parenteral therapy followed by oral agents, it is important to try to accurately identify the underlying microorganism(s). The optimal duration of antibiotic therapy for diabetic foot osteomyelitis is uncertain. A systematic review of treatment of osteomyelitis in patients with and without diabetes [79] found that there was no evidence that antibiotic therapy for more than 4–6 weeks improves outcomes compared with shorter regimens, including for the diabetic foot (Table 2). We share this view [62,70,80].

Established wisdom has held that diabetic foot osteomyelitis, like most chronic bone infections, requires surgical debridement or resection of necrotic and infected bone. For example, in a study of 50 patients with chronic toe osteomyelitis, patients who underwent surgical resection had a significantly lower relapse rate [81]. There are, however, hundreds of reports of apparently successful treatment without surgery, with most series reporting remission rates of 60% to 70% [82,83]. Thus, when the patient or the medical team prefer to avoid surgery, a trial of exclusively antibiotic therapy may be reasonable. But, the advantages of surgical therapy (especially in case of toe amputations), including the relatively short lengths of hospital stay, reduced antibiotic consumption and likely higher remission rates, should be weighed against the potential risks.

Hyperbaric Oxygen Therapy and Stimulating Factors

The value of hyperbaric oxygen therapy for non-infected diabetic ulcers is a question of ongoing debate [80,84–86]. A 2012 Cochrane systematic review concluded that hyperbaric oxygen therapy significantly increased ulcer healing in the short term but not the long term, but because of the flawed trials they were not confident in the results [87]. Some suggest that hyperbaric oxygen decreases rates of lower extremity amputation in patients with diabetic foot ulcers or postsurgical amputation wounds in persons with diabetes, and facilitates ulcer healing [88]. There are, however, no published data directly related to the effect of hyperbaric oxygen therapy for infectious aspects (either soft tissue or bone) of the diabetic foot [84].

Several studies have examined the usefulness of adjunctive treatment of DFIs with granulocyte-colony stimulating factors. A Cochrane systematic review of the five eligible trials concluded that these treatments did not increase the likelihood of resolution of infection but did appear to reduce the need for surgical interventions, especially amputations, and the duration of hospitalization. Studies of platelet-derived [89] and other growth factors and skin substitutes have not shown any specific benefit regarding resolution or prevention of infection [90,91].

Antiseptic Dressings and Other Topical Treatments

Several studies have assessed topical treatments in patients with diabetic foot ulcers and, to a lesser extent, for DFI. For the majority, ulcer healing rather than resolution or prevention of infection was the primary outcome of interest. Most of the studies evaluated topical antiseptic agents (e.g. silver, povidone iodine, hypochlorite, peroxide, zinc oxide) as adjuncts to other standard treatments. None of these agents has been proven to provide superior outcomes compared to other non-antiseptic dressings [92]. Similarly, recent systematic reviews have failed to detect a superiority of various other dressings, such as foam [93,94], hydrocolloid [95] and alginate [96], for ulcer healing or resolution of infection. A review of topical antimicrobial therapy for treating chronic wounds concluded that there are few proven indications for any of the currently available agents [91].

Two topical antimicrobial agents have been investigated for DFIs. A large randomized controlled trial in patients with a mild DF showed that treatment with a topical antimicrobial peptide (pexiganan) produced clinical outcomes similar to

those of an oral antibiotic (ofloxacin) [74]. In an open-label study, daily application of a gentamicin-collagen sponge for up to 28 days in combination with systemic antibiotic therapy was compared to systemic antibiotic therapy alone in the treatment of moderate DFIs [97]. Although this study failed to meet its primary endpoint (percent of patients with an outcome of clinical cure at day 7 of treatment), the gentamicin-collagen sponge showed superior efficacy in eradicating baseline pathogens and achieving clinical cure at the final visit [97].

Vacuum-Assisted Negative-Pressure Therapy

While widely used for accelerating wound healing, there are limited published data on the effectiveness of vacuum-assisted negative-pressure therapy on DFI, including osteomyelitis [98]. Concerning diabetic foot ulcers, a systematic review identified four randomized trials [99]. While all, including a multicentre study that enrolled 342 patients [100], found that vacuum-assisted therapy was more effective than conventional dressings, the quality of each of the studies was weak and the outcomes studied and patient selection were divergent [99,101].

Off-Loading

Off-loading pressure is a critical part of the treatment of almost all diabetic foot ulcers, including those that are infected [102]. While the principle of off-loading is easy to understand, in practice it greatly depends on near total compliance on the part of the patient. The criterion standard for off-loading is the total contact cast, which is associated with ulcer healing rates of over 90% [102]. The main advantage of this device may be that the patient cannot easily remove it. Given the high recurrence rates of neuropathic foot ulcers, new approaches include helping patients to modify their walking pattern over the long term, perhaps with feedback-based approaches [103].

Clinical Pathways, Guidelines and Bundle Interventions

DFIs exemplify a multifaceted problem that particularly benefits from a multidisciplinary approach [7]. In the past decade, several evidence-based DFI guidelines have been published that provide an approach to optimize outcomes [7,104] and to avoid amputations [105]. All consistently address the critical role of multidisciplinary teams involving specialists such as diabetologists, orthopaedic/podiatric surgeons, infectious diseases specialists, vascular surgeons, angiologists, interventional radiologists, specialized nurses and physiotherapists; such teams have been established in many large hospitals in resource-rich countries all over the world [7,13]. These teams have been shown to be beneficial in avoiding adverse outcomes in both inpatients and outpatients in many studies. They are, however, hampered by several logistic problems: (a) it is often difficult to bring the members of the multidisciplinary team together outside of a fixed meeting time; (b) the number of patients requiring evaluation often exceeds the capacity of fixed multidisciplinary meetings; and (c) members of the team often turnover. For example, at Geneva University Hospitals, there is a 45-min diabetic foot team meeting weekly, but we have

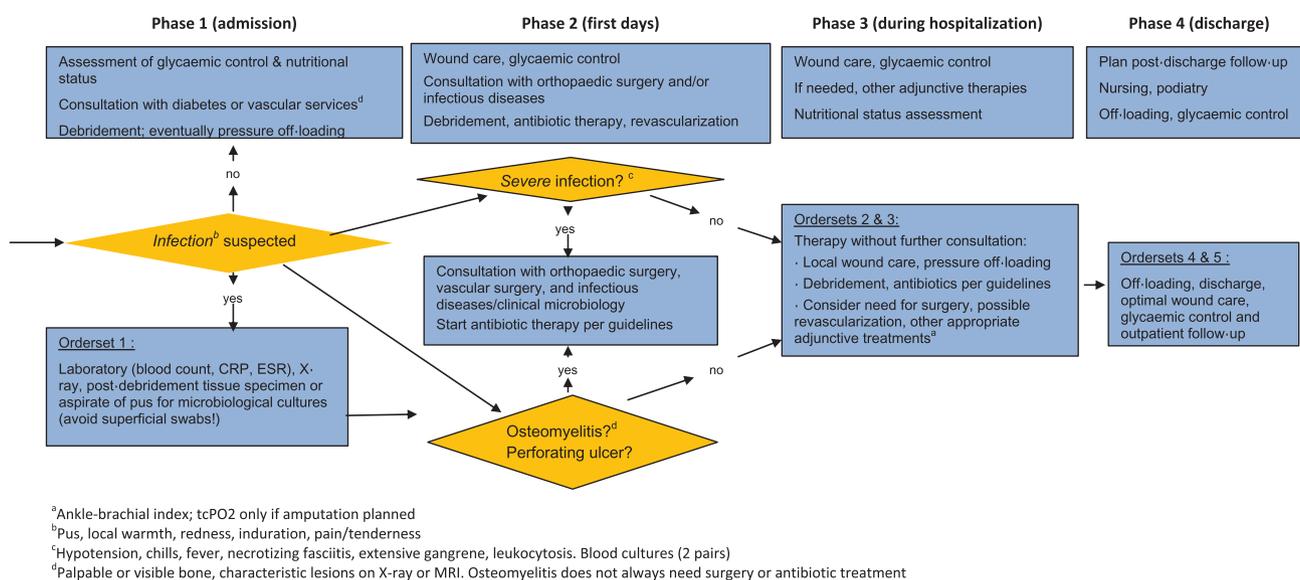


Figure 2. Schema of the clinical pathway for the infected diabetic foot, Geneva University Hospitals.

observed that team meetings are time-consuming, key members are frequently absent and the teams are often not able to rapidly assess all of the DFI patients in need of evaluation and care.

To provide the advantages of a multidisciplinary DFI team while attempting to overcome some of its logistic problems, we are developing, and plan to evaluate, a clinical pathway (with electronic ordersets) to aid all healthcare providers in both our outpatient and inpatient settings. Ordersets are a modern and powerful tool to implement ‘bundles’ (a package of procedures) and to change processes to encourage and facilitate optimal and evidence-based care. They have proven efficacy in several fields of medicine [106], are practical, easy to implement and, unlike classical campaigning, may show a sustained effect over time [104–108]. Clinical pathways provide an easy and cost-effective way to instruct physicians, surgeons, nurses and other healthcare workers on what diagnostic and therapeutic interventions are available and most appropriate and, combined with ordersets, make it easy and quick to do the right thing. If they are coupled with the electronic computerized prescription programs and the hospitals’ antibiotic stewardship program, ordersets may increase our understanding of the number, types and outcomes of treatment of DFI in a given hospital. This may uncover problems related to improper diagnostic or therapeutic approaches, or bottlenecks in providing optimal care. Moreover, they might help to optimize (and minimize) use of antibiotic agents in patients with a DFI.

Figure 2 shows a draft of a DFI clinical pathway that we are implementing at Geneva University Hospitals. This pathway provides guidance for dealing with infectious aspects of diabetic foot wounds for hospitalized patients. Of note, many of these patients may have other non-infectious diabetes-related complications and may need other specialized care, such as from a wound specialist, podiatrist or diabetologist. The aims of this pathway are to: (a) facilitate the flow of care for hospitalized patients with a diabetic foot infection; (b) encourage and facilitate an evidence-based diagnostic work-up

and approach to treatment, including avoiding unnecessary examinations and therapies. This schema is based on the guidelines developed by the Infectious Diseases Society of America for diabetic foot infections [13].

In summary, DFIs are a common, complex and costly problem. Clinical research over the past decade has markedly increased our understanding of the epidemiology, pathophysiology diagnosis and treatment of both soft tissue and bone infections. These have allowed the development of evidence-based and validated guidelines. The task now is to implement these guidelines, to audit the process and outcomes in individual settings and to continue to look for ways to improve care.

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Conflict of Interest

K. G. and Z. P. declare no conflict of interest. B. A. L. has served as a consultant to KCI, Innocoll, Dipexium. I. U. has received research funding from Innocoll.

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