Understanding Infection

4

Felix W. A. Waibel and İlker Uçkay

Key Points

- The diagnosis of infection in the diabetic foot is based on clinical aspects (with eventually radiology for osteomyelitis), not on the microbiology of superficial swabs or serum inflammatory markers.
- The treatment of diabetic foot infections is multidisciplinary, of which iterative debridement and wound care, systemic antibiotic therapies, and adequate offloading are the cornerstones.
- Most antibiotic therapies can be administered orally and for relatively short periods (approximately 10 days for soft tissue infections, 4–6 weeks for unresected bone).
- The risk for therapy failures and long-term recurrences is high. Therefore, the prevention of infection, corrective and reconstructive surgeries of the altered foot anatomy, and the overall improvement of the patient's compliance is more important than single therapeutic approaches.

4.1 Introduction

Diabetic foot infections (DFI), including diabetic foot osteomyelitis (DFO), are frequent entities with a lifetime risk of 25% among all adult patients with diabetes mellitus [1]. Being almost always the consequence of ulcers secondary to neuro- and vasculopathy, they have a high risk of lower extremity amputation (due to vascular reasons) [2]. Soft tissue closure is important to protect underlying structures from infection, while a persisting infection leads to flap failure. Hence, the reconstruction should be performed without persisting infection [3]. There have been many new insights on the microbiology, diagnosis, and treatment of DFIs, although the implementation of this knowledge into clinical practice has been suboptimal. Today, employing evidence-based guidelines, multidisciplinary teams, and institution-specific clinical pathways helps guide optimal care of this multifaceted problem. Patients are more often treated in the ambulatory setting, with antibiotic regimens that are more targeted, oral and shorter course, and with more conservative (but earlier) surgical interventions.

F. W. A. Waibel
Department of Orthopedic Surgery, Balgrist University Hospital, Zürich, Switzerland
e-mail: felix.waibel@balgrist.ch

İ. Uçkay (✉)
Infectiology, Clinical Research UCAR, Balgrist University Hospital, Zürich, Switzerland
e-mail: ilker.uckay@balgrist.ch

J. P. Hong, H. Suh (eds.), *Diabetic Foot Reconstruction*,
https://doi.org/10.1007/978-981-16-9816-3_4

New diagnostic and therapeutic methods are being developed at an accelerating pace [4]. This chapter reviews the diagnosis and treatment of DFI, including for DFO.

4.2 Infection Matters Regarding Diabetic Foot Reconstruction

Plastic reconstruction in diabetic feet is linked to DFI in mutual ways. On the prevention side, surgeons reconstruct to restore an intact skin barrier that ultimately protects deep structures from infection [3]. The functioning diabetic flap may significantly increase the overall 5-year survival of the affected diabetic foot, when compared to patients with direct major amputations from the start [5, 6]. On the therapeutic side, the absence of an underlying infection is of paramount importance for graft survival [3]. Hence, the first step in the diabetic foot reconstruction is infection control [7, 8]. Any infected soft tissue or bone must be removed [7, 9, 10]. A systematic review of 18 studies identified infection as the main cause for early flap loss [11] in contrast to non-infected flaps, for which anastomotic failures, local thromboses, and local arteriopathies [12] remain the main causes of flap failure [11].

4.3 Diagnosing Infection

A variety of classifications has been proposed for DFIs, mostly being part of broader classifications for diabetic foot ulcers [1, 13, 14]. 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 and guide therapy. The IWGDF-PEDIS-classification (an acronym standing for perfusion, extent [size], depth, infection, and sensation/neuropathy) suggests a semi-quantitative four-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 [13].

Of note, superficial microbiological culture results alone do not define infection, because all open wounds are colonized with microorganisms. Even quantitative microbiological results such as the presence of $\geq 10^5$ colony forming units/gram of tissue do not define DFI. In consequence, the diagnosis of DFI must base on clinical findings: new or progressive redness, warmth, induration, pain, tenderness and/or purulence (see Fig. 4.1). Some authors suggest to add findings like wound friability, undermining or poor granulation tissue, foul odor or unexpectedly slow healing as signs of infection. Of note, many of these signs are subjective and can be provoked by other non-infectious differential diagnoses such as acute gout, acute ischemia, or acute Charcot neuro-arthropathy [15, 16]. Contrary to many soft tissue infections outside of the diabetic foot, systemic inflammatory signs (fever, chills, hypotension, delirium), elevated serum inflammatory markers (leukocytosis, sedimentation rate (ESR), C-protein, pro-calcitonin) and positive blood cultures are unusual in (chronic) DFI [16, 17]. Microbiological tests from deep infected tissues, bone, or franc pus depict the cornerstone in diagnosis and guidance of DFI treatment. In order to avoid false-positive results due to colonizing species, only deep (intraoperative) samples should be taken after cleaning and the debriding the wound. The best material would be non-necrotic tissue or even pus from deep.

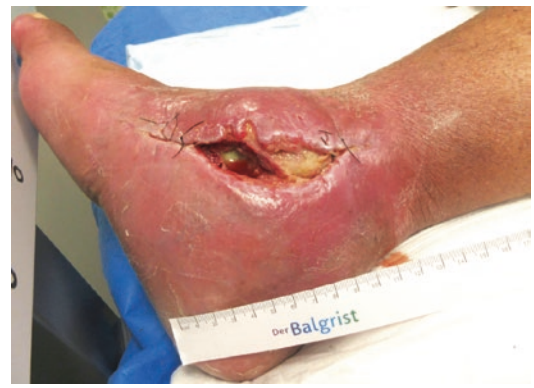

Fig. 4.1 Right foot of a 62-year-old male patient with a diabetic Charcot foot. Soft tissue infection and underlying osteomyelitis. Please note the large wound over the medial hindfoot with frayed wound borders. At the bottom of the wound, a cement spacer can be seen. Image published with the permission of the patient

Superficial microbiological swabs are futile [16], as they reveal more different bacteria (contamination or colonizing bacteria most likely) than deep tissue samples and miss many pathogens like anaerobic bacteria [16, 18].

The only virtually pathognomonic clinical sign for the diagnosis of DFO is the presence of fragments of bone discharging from a wound. This is only possible in advanced infections related to ulcers; and rare. Usually, a DFO is suspected and later confirmed. Blood tests have little value in diagnosing DFO. Large, deep, or chronic wounds (persisting for ≥3 months) or red and swollen toes ("sausage toe") should raise the suspicion of DFO. A simple diagnostic approach is the probe-to-bone test. The clinician uses a sterile blunt metal probe to determine, whether bone can be palpated through the diabetic foot ulcer. A negative test does not completely rule out DFO, while a positive test has high predictive value for bone infection [19, 20]. Although needle puncture of deep soft tissue near bone does not reliably predict the results of bone cultures, puncture of the bone itself may be an easy way to obtain bone culture at the bedside [21]. When DFO is suspected, two separate positive deep bony microbiological samples showing the same bacteria may sometimes confirm the DFO [22]. One or two weeks of "antibiotic free window" before biopsy or surgery are recommended to avoid false-negative results if chronic DFO is suspected [23]. Of note, the microbiological confirmation of DFO is not necessary when the infected area is amputated in toto [24].

Concerning imaging, plain radiographs should be the first imaging modality for every DFI and DFO. Erosions of the osseous borders are characteristic for DFO [25]. Further signs are periosteal reactions or elevations, regional osteopenia or trabecular bone patterns, especially in the calcaneum [26]. Sensitivity of the plain radiography in diagnosing DFO is low, with one review citing a pooled sensitivity of 0.54 and a specificity of 0.68 [27]. Computed tomography (CT) can guide surgical planning and combine a good sensitivity and better prize-quality ratio than Magnetic Resonance Imaging (MRI) [28]. MRI has a good sensitivity (93%) and a high specificity (79%) for diagnosing DFO prior to surgical treatment [29], but is less easily available than standard X-rays, and relatively expensive. Nuclear medicine techniques are less used since the MRI gained momentum throughout the world [30].

4.3.1 Main Pathogens

Aerobic gram-positive cocci (*Staphylococcus aureus* or β-streptococci) remain the main pathogens of community-acquired DFI in temperate areas such as Central Europe or North America [16, 31]. Depending on geographical location, prevalence of distinct pathogens is different. In many arid and tropical areas, *S. aureus* is less prevalent and gram-negative rods like *Pseudomonas aeruginosa* prevail [16]. The reasons for this geographical difference have 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 [16]. Chronic infected wounds demonstrate polymicrobial infection. An increasing likelihood has been observed for multidrug resistant organisms (MDROs) in DFI [32–34]. The leading multi-resistant pathogen in this regard has been health care-associated methicillin-resistant *S. aureus* (MRSA) two decades ago in many regions of the world. However, the current literature reports decreasing prevalence of MRSA in most countries [35]. Greater actual concern has been raised by multi-resistant gram-negative organisms that produce extended-spectrum β-lactamases or carbapenemases. The impact of fungi in DFI is anecdotic [33, 36, 37].

4.4 Management of Diabetic Foot Infection

4.4.1 Initial Multidisciplinary Approach

Generally, DFIs require a multidisciplinary approach, of debridement (or professional wound care), systemic antibiotic therapy and off-loading are the minimal cornerstones [38]. Revascularization of macroangiopathic arterial stenoses, before or after the surgical intervention, is frequently needed in up to 20% of DFIs [16]. The vascular assessment is highlighted in Chaps. 2 and 7. A first surgical drainage-debridement is particularly important for abscesses, necrotizing fasciitis and for a substantial proportion of DFO cases [39]. Procedures, such as the correction of foot deformities, arthrodesis [40] or combination of correction and debridement for infection [41], may serve to prevent future DFIs. Chaps. 5 and 6 resumes surgical debridement (Chap. 5) and deformity correction (Chap. 6) in detail. Table 4.1 resumes key aspects in the previous and modern managements of DFI.

4.4.2 Antibiotic Therapies for Soft Tissue Infections of the Diabetic Foot

We need systemic antibiotic therapy for the treatment of DFI. As it may fail as a sole modality, it is usually combined with one or more surgical procedures, off-loading and proper wound care. Initial antibiotic treatment is empirical in most cases. It bases on epidemiological features, knowledge of the local resistance patterns, and the infection severity [38]. Several principles help selecting an appropriately regimen [42]. In case of severe infections, or if the patient has failed to respond to a prior narrower-spectrum antibiotic regimen, therapy could target presumed Gram-negative pathogens as well. In case of gangrenous wounds, antibiotics covering anaerobes are recommended [18, 42]. If cultures grow multiple organisms, it is often sufficient to treat the major pathogens (e.g., *S. aureus*, streptococci, *Enterobacteriaceae*). Skin pathogens (coagulase-negative staphylococci, corynebacteria, or *Bacillus* spp.) can be dismissed in most cases, especially in the absence of osteosynthetic

Table 4.1 Key elements in the management of diabetic foot infections (*authors' personal summary*)

Research field	Established today	Potential developments in the future
Pathogens of concern	*Staphylococcus aureus*, streptococci	Multidrug resistant organisms. Gram-negative pathogens in (sub)tropical climates
Microbiological diagnosis	Standard cultures, usually of swab specimens	No changes, except research of microbioma for academic reasons
Imaging	Plain X-rays	Magnetic resonance imaging for preoperative planification?
Antibiotic agents	Amino-penicillins, cephalosporins, fluoroquinolones	Antibiotic stewardship efforts, carbapenems, rifampicin?
Route of administration	Initial intravenous administration, usually in hospital	Oral (sometimes after brief intravenous course)
Duration of antibiotic therapy	Few weeks for soft tissues; ≥6–12 weeks for bone	1–2 weeks for soft tissue infections, 3–6 weeks for osteomyelitis
Surgical approach	Aggressive (ablative) therapeutic surgery; inpatient	Corrective and reconstructive surgery
Revascularization	Open vascular surgery	More percutaneous angioplasty
Management	Mostly individual, empirical approaches	Guidelines based on systematic reviews. Multidisciplinary teams
Scientific publications	Mostly case series and epidemiological surveys	More prospective randomized trials, multicenter studies

Adapted from reference Uçkay et al. [4]

material [43, 44]. Likewise, skin colonization with health-care-associated MRSA does not necessitate empiric coverage of this organism, even in the presence of foreign material [45, 46].

As most DFI go along with some degree of peripheral arterial disease, the question remains whether antibiotic agents penetrate sufficiently. Standard doses of most β-lactam antibiotics achieve relatively low but likely therapeutic tissue levels. Clindamycin, fluoroquinolones, linezolid, rifampin, and to some degree, tetracyclines and co-trimoxazole offer good oral bioavailability together with an acceptable penetration in bone, synovia, biofilm, and necrotic tissue [22, 43]. In consequence, oral absorption of commonly used antibiotics is usually sufficient for oral antibiotic therapy in mild to moderate DFIs [47]. Randomized trials in DFI have failed to show superiority of one particular antibiotic agent or route of administration [48–50]. Today, the evidence is too weak to recommend any particular antimicrobial agent [51] or any particular route of delivery or duration of antibiotic therapy [52, 53]. Currently, the authors of this Chapter lead two randomized trials investigating shorter durations in DFI and DFO [54]. Table 4.2 displays suggested antibiotic regimens based on the IDSA guidelines [55].

4.4.3 Topical Anti-infective Wound Care for Soft Tissue Infections of the Diabetic Foot

Many studies have assessed topical disinfectants or antiseptics for the treatment of DFI, including compounds with silver, povidone, or hypochlorite [4]. The majority of these studies used ulcer healing, rather than resolution or prevention of infection, as the primary outcome. None of these agents has demonstrated superior outcomes compared to non-antiseptic dressings. Likewise, recent systematic reviews have found that various other dressings, such as foam, hydrocolloid, or alginate, offer no advantage over other dressings for ulcer healing or resolution of infection [4]. Thus, as was true three decades ago, dressing changes with simple gauze and saline solution alone appears to be sufficient for most patients.

4.4.4 Management of Necrotizing Fasciitis of the Diabetic Foot

Usually, DFI soft tissue infections evolve during several days before becoming dangerous [56]. In contrast, a special clinical entity among the groups of soft tissue DFI is “necrotizing fasciitis”

Table 4.2 Suggested antibiotic regimens (*author’s choices*)

Severity of infection	Expected pathogens	(Empirical) antibiotic agents	Administration route
Mild	*S. aureus*, Streptococci	Cephalosporins, clindamycin, co-amoxiclav	Oral
Moderate	*S. aureus*, Streptococci *Enterobacteriaceae*	Co-amoxiclav	Oral or parenteral (to start)
Severe	All pathogens,	Co-amoxiclav, piperacillin-tazobactam, carbapenem	Parenteral, with later oral switch when stable
Bacteremic	No empiric therapy, since pathogen known	Based on culture and sensitivity results	Parenteral
Chronic osteomyelitis	All pathogens	Based on bone culture	Oral

Inspired from the reference Lipsky et al. [55]

(NF). NF is an hyper-acute soft tissue infection. We have never witnessed a NF issuing from a chronic DFO. Plastic surgery is particularly involved with reconstruction in the aftermath of infection. The rapid tissue necrosis often leads to systemic sepsis, toxic-shock-like syndrome and multi-organ failure. NF in diabetic patients is usually polymicrobial and most often involves both aerobic organisms (especially *Streptococcus pyogenes*) [57]. Using multivariable analysis, one study of patients with NF found that the presence of diabetes was associated with a significantly increased risk of amputation [57]. Treatment of NF requires rapid fluid and electrolyte corrections, hemodynamic stabilization, support for failing organ systems and appropriate parenteral antibiotic therapy. Several different regimens of antibiotics have been recommended, and the choice may be institution dependent. In general, we consider broad-spectrum agents, such as piperacillin-tazobactam, or carbapenems, or vancomycin MRSA is suspected. In addition, early aggressive surgical debridement (often repeated to ensure all necrotic tissue has been removed) is usually necessary. Various adjunctive treatments, including hyperbaric oxygen therapy or intravenous immunoglobulins, have been used, but the efficacy of each is unclear [57].

4.4.5 Antibiotic Treatment for Non-amputated Diabetic Foot Osteomyelitis

As non-resected DFOs genuinely require long antibiotic treatments, it is important to identify the underlying pathogen(s). The optimal duration of antibiotic therapy for DFO is uncertain. A systematic review of chronic osteomyelitis in adult patients, with and without diabetes, found no evidence for a better outcome with antibiotic therapies for more than 4–6 weeks compared with shorter regimens, including for the diabetic foot [58]. In the diabetic foot, a recent single-center evaluation with 1018 episodes of DFI and DFO equally failed to determine an optimal duration of systemic antibiotic administration in terms of remission of infection [59]. A small, randomized-controlled study found that 6 weeks compared with 12 weeks of treatment of diabetic foot osteomyelitis produced similar results [60].

There are hundreds of reports of apparently successful treatment without surgery. Thus, when the patient or the medical team prefers to avoid surgery, a trial of exclusively antibiotic therapy is 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. The risk of clinical and radiological failures of the conservative approach for DFO is around 30–40% [61], albeit if the proportion of microbiological recurrences (with the same pathogens as in the index episode) is lower with approximately 20% [61]. In case with concomitant severe ischemia it might be higher.

Ideally, the treatment of DFO contains surgical debridement, or the resection of necrotic and infected bone (total amputation). A study of 50 patients with chronic toe DFO showed that patients with surgical resections had a significantly lower relapse rate [62]. This was also witnessed in the aforementioned single-center survey with partial amputations [59]. In well-selected patients and neuropathic DFO cases without progressive ischemia, other studies report successful treatment without surgery, with selected remission rates of 60–70% [63, 64]. When surgery is avoided for different reasons, a trial of exclusively antibiotic therapy may be reasonable. But generally, the advantages of concomitant surgical therapy, such as the reduced antibiotic consumption and higher remission rates in the average DFI patient, should be weighed against the potential risks. Of note, the proportion of antibiotic-related side effects in randomized-controlled DFI trials during a week-long therapy may compromise up to 20–30% of all DFO regimens [65]. Lastly and most importantly, in the wake of persisting underlying osteomyelitis as the main identified reason for flap failure [11], a definitive surgical removal of infected bone is paramount when reconstructive plastic surgery is planned.

4.4.6 Antibiotic Management Before and After Reconstruction

The different antibiotic approaches around the timing of elective plastic reconstruction are not evidence-based and should be subject of future research. Today, this antibiotic policy depends on the preference of the treating plastic surgeon. Some reconstruct under current antibiotic therapy and continue the therapy afterwards. Others swab the ulcer surface (often several times) to ensure the near-absence of potential pathogens colonizing the future site, and frequently postpone the elective surgery. A third group of surgeons stop eventual therapeutic antibiotics before elective reconstruction and re-start therapy after reconstruction; with the opportunity to perform intraoperative samples non-selected by ongoing antibiotic therapies.

The authors of this chapter have the following opinion: We avoid superficial sampling of future reconstruction sites before elective surgery, unless there is real, clinical, infection. The presence of bacteria in superficial samples of skin breakdowns depends on the laboratory and the localization of swabbing, and is influenced by chance. All chronic lesions are colonized with various bacteria that can just differ by the localization. This colonization does not correlate with the microorganisms of eventual future surgical site infections. Moreover, such a blind swabbing policy postpones surgery in case of positive findings which is costly and cumbersome for the hospital and patients. Instead, we propose an "antibiotic-free window" of several days before elective surgery, to sample 2–4 deep tissue specimens (not swabs) during reconstruction, and to start an empirical antibiotic therapy (if clinically necessary). This therapy can be switched to oral antibiotic regimens targeted on the intraoperative findings. The widespread intravenous administration is not necessary in the absence of franc infection (pus, cellulitis, etc.).

The post-reconstruction antibiotic therapy is justified in case of massive contamination of the surgical site, of which the duration depends on the intraoperative visual aspects, the chronicity of the problem and the past history of local and recurrent infection. The minimal post-reconstruction antibiotic duration relies on the experience of the surgeon. It can be as short as 3 days (in analogy to acute open fractures [66]) or prolonged for some days. In any case and according to current knowledge, the utmost duration is 6 weeks (unless the infection is due to mycobacteria, actinomyces, or fungi). In osteoarticular infectiology, any antibiotic administration beyond 6 weeks for usual pyogenic bacteria is futile [67]. Because after this time, chemistry alone will not heal the problem without new surgical debridement. This utmost limit of 6 weeks is valid for every plastic surgery, even for sacral osteomyelitis coverage with higher risks of recurrence than for diabetic foot plastic surgery [68].

4.5 Adjunctive Treatments

4.5.1 Hyperbaric Oxygen Therapy

The value of hyperbaric oxygen therapy (HBOT) for DFI continues to be hotly debated. A 2012 Cochrane systematic review concluded that HBOT significantly increased ulcer healing in the short term, but not the long term; because of the flawed trials, however, they were not confident in the results [69]. Some studies suggest that HBOT facilitates wound healing and decreases rates of lower extremity amputation in diabetic patients with a foot ulcer or postsurgical amputation wound, but most experience is retrospective and non-comparative. There are, however, no published data directly related to the effect of HBOT for infectious aspects (either soft tissue or bone) of the diabetic foot [4].

4.5.2 Off-Loading

Off-loading pressure from an ulcer is critical to getting it to heal, including those that are infected [4]. This was, is, and will be the cornerstone of both treatment and secondary prevention. The criterion standard method for off-loading, the total contact cast, leads to ulcer healing in over 90% of

cases, and has been available for decades. For patients with little or no foot deformity, prefabricated extra depth footwear with a stiff rocker bottom walking sole is usually sufficient. Cases with moderate deformity may require custom-made shoes with custom-molded, full contact insoles. Off-loading can be partial and surgical, e.g., performing a flexor-tenotomy in a patient with claw toes. An elective surgical approach may be right when conservative therapy has failed to prevent severe deformity or joint instability or in the presence of ulcerating hammer and claw toes. Clinicians should generally explain to the patient the benefit of off-loading [4].

4.6 Conclusion

The diagnosis of DFI is based on clinical aspects (with additional radiology for DFO); not on the microbiology of superficial swabs or serum inflammatory markers. The microbiology identifies the pathogens and is of confirmatory nature regarding the diagnosis in the soft tissues, but decisive for the bone. The treatment is multidisciplinary resuming iterative debridement, surgery in its multiple forms, professional wound care, antibiotic therapy, strict off-loading, and eventual revascularization. Most antibiotics can be given orally for approximately 1–2 weeks for soft tissue infection, and during 4–6 weeks for unresected DFO. The risk for treatment failures and infectious recurrences is high. Prevention of infection, as well as reconstructive surgeries of the altered foot, is very important.

Disclosure Statement We have nothing to disclose and no conflict of interests. There is no funding for this chapter.

References

1. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293:217–28.
2. Zingg M, Nicodème JD, Uçkay I, Ray A, Suva D. Lower limb amputation: indication, preoperative workup and complications. Rev Med Suisse. 2015;10:2409–13.
3. Clemens MW, Attinger CE. Functional reconstruction of the diabetic foot. Semin Plast Surg. 2010;24:43–56.
4. Uçkay I, Aragón-Sánchez J, Lew D, Lipsky BA. Diabetic foot infections: what have we learned in the last 30 years? Int J Infect Dis. 2015;40:81–91.
5. Oh TS, Lee HS, Hong JP. Diabetic foot reconstruction using free flaps increases 5-year-survival rate. J Plast Reconstr Aesthet Surg. 2013;66:243–50.
6. Sato T, Yana Y, Ichioka S. Free flap reconstruction for diabetic foot limb salvage. J Plast Surg Hand Surg. 2017;51:399–404.
7. Suh HS, Oh TS, Hong JP. Innovations in diabetic foot reconstruction using super-microsurgery. Diabetes Metab Res Rev. 2016;32:275–80.
8. Attinger CE, Bulan EJ. Débridement. The key initial first step in wound healing. Foot Ankle Clin. 2001;6:627–60.
9. Gonzalez MH, Weinzweig N. Muscle flaps in the treatment of osteomyelitis of the lower extremity. J Trauma. 2005;58:1019–23.
10. Ha Van G, Siney H, Danan J-P, Sachon C, Grimaldi A. Treatment of osteomyelitis in the diabetic foot: contribution of conservative surgery. Diabetes Care. 1996;19:1257–60.
11. Fitzgerald O'Connor EJ, Vesely M, Holt PJ, Jones KG, Thompson MM, Hinchliffe RJ. A systematic review of free tissue transfer in the management of non-traumatic lower extremity wounds in patients with diabetes. Eur J Vasc Endovasc Surg. 2011;41:391–9.
12. Kim HB, Altıparmak M, Pak CJ, Suh HP, Hong JP. Reconstruction using free flaps for diabetic heel defects: outcomes and risk factor analysis. J Reconstr Microsurg. 2020;36:494–500.
13. Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. Diabetes Metab Res Rev. 2004;20:90–5.
14. Chuan F, Tang K, Jiang P, Zhou B, He X. Reliability and validity of the perfusion, extent, depth, infection and sensation (PEDIS) classification system and score in patients with diabetic foot ulcer. PLoS One. 2015;10:0124739.
15. Berli M, Vlachopoulos L, Leupi S, Böni T, Baltin C. Treatment of Charcot Neuroarthropathy and osteomyelitis of the same foot: a retrospective cohort study. BMC Musculoskelet Disord. 2017;18:460.
16. Uçkay I, Gariani K, Pataky Z, Lipsky BA. Diabetic foot infections: state-of-the-art. Diabetes Obes Metab. 2014;16:305–16.
17. Uçkay I, Garzoni C, Ferry T, Harbarth S, Stern R, Assal M, et al. Postoperative serum pro-calcitonin and C-reactive protein levels in patients with orthopedic infections. Swiss Med Wkly. 2010;140:13124.
18. Charles PG, Uçkay I, Kressmann B, Emonet S, Lipsky BA. The role of anaerobes in diabetic foot infections. Anaerobe. 2015;34:8–13.
19. Butalia S, Palda VA, Sargeant RJ, Detsky AS, Mourad O. Does this patient with diabetes have osteomyelitis of the lower extremity? JAMA. 2008;299:806–13.

20. Aragón-Sánchez J, Lipsky BA, Lázaro-Martínez JL. Diagnosing diabetic foot osteomyelitis: is the combination of probe-to-bone test and plain radiography sufficient for high-risk inpatients? Diabet Med. 2011;28:191–4.
21. Senneville E, Morant H, Descamps D, Dekeyser S, Beltrand E, Singer B, et al. Needle puncture and transcutaneous bone biopsy cultures are inconsistent in patients with diabetes and suspected osteomyelitis of the foot. Clin Infect Dis. 2009;48:888–93.
22. Bernard L, Assal M, Garzoni C, Uçkay I. Predicting the pathogen of diabetic toe osteomyelitis by two consecutive ulcer cultures with bone contact. Eur J Clin Microbiol Infect Dis. 2011;30:279–81.
23. Govaert GAM, Kuehl R, Atkins BL, Trampuz A, Morgenstern M, Obremskey WT, et al. Diagnosing fracture-related infection: current concepts and recommendations. J Orthop Trauma. 2020;34:8–17.
24. Rossel A, Lebowitz D, Gariani K, Abbas M, Kressmann B, Assal M, et al. Stopping antibiotics after surgical amputation in diabetic foot and ankle infections—a daily practice cohort. Endocrinol Diabetes Metab. 2019;2:00059.
25. Álvaro-Afonso FJ, Lázaro-Martínez JL, Aragón-Sánchez J, García-Morales E, Cecilia-Matilla A, Beneit-Montesinos JV. Interobserver and intraobserver reproducibility of plain X-rays in the diagnosis of diabetic foot osteomyelitis. Int J Low Extrem Wounds. 2013;12:12–5.
26. Waibel FWA, Uçkay I, Sairanen K, Waibel L, Berli MC, Boni T, et al. Diabetic calcaneal osteomyelitis. Infez Med. 2019;27(3):225–38.
27. Newman LG, Waller J, Palestro CJ, Schwartz M, Klein MJ, Hermann G, et al. Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. JAMA. 1991;266(9):1246–51.
28. Pineda C, Espinosa R, Pena A. Radiographic imaging in osteomyelitis: the role of plain radiography, computed tomography, ultrasonography, magnetic resonance imaging, and scintigraphy. Semin Plast Surg. 2009;23:80–9.
29. Lauri C, Tamminga M, Glaudemans A, Juarez Orozco LE, Erba PA, Jutte PC, et al. Detection of osteomyelitis in the diabetic foot by imaging techniques: a systematic review and meta-analysis comparing MRI, white blood cell scintigraphy, and FDG-PET. Diabetes Care. 2017;40:1111–20.
30. Glaudemans AW, Uçkay I, Lipsky BA. Challenges in diagnosing infection in the diabetic foot. Diabet Med. 2015;32:748–59.
31. Gardner SE, Hillis SL, Heilmann K, Segre JA, Grice EA. The neuropathic diabetic foot ulcer microbiome is associated with clinical factors. Diabetes. 2013;62:923–30.
32. Byren I, Peters EJ, Hoey C, Berendt A, Lipsky BA. Pharmacotherapy of diabetic foot osteomyelitis. Expert Opin Pharmacother. 2009;10:3033–47.
33. Boyanova L, Mitov I. Antibiotic resistance rates in causative agents of infections in diabetic patients: rising concerns. Expert Rev Anti-Infect Ther. 2013;11:411–20.
34. Djahmi N, Messad N, Nedjai S, Moussaoui A, Mazouz D, Richard JL, et al. Molecular epidemiology of *Staphylococcus aureus* strains isolated from inpatients with infected diabetic foot ulcers in an Algerian University Hospital. Clin Microbiol Infect. 2013;19:398–404.
35. Zenelaj B, Bouvet C, Lipsky BA, Uçkay I. Do diabetic foot infections with methicillin-resistant *Staphylococcus aureus* differ from those with other pathogens? Int J Low Extrem Wounds. 2014;13:263–72.
36. Bader M, Jafri AK, Krueger T, Kumar V. Fusarium Osteomyelitis of the Foot in a Patient with Diabetes Mellitus. Scand J Infect Dis. 2003;35:895–7.
37. Missoni EM, Kalenić S, Vukelić M, De Syo D, Belicza M, Kern J, et al. [Role of yeasts in diabetic foot ulcer infection]. Acta Med Croatica 2006;60:43–50.
38. Ertuğrul B, Uçkay I, Schöni M, Peter-Riesch B, Lipsky BA. Management of diabetic foot infections in the light of recent literature and new international guidelines. Expert Rev Anti-Infect Ther. 2020;18:293–305.
39. Widatalla AH, Mahadi SE, Shawer MA, Mahmoud SM, Abdelmageed AE, Ahmed ME. Diabetic foot infections with osteomyelitis: efficacy of combined surgical and medical treatment. Diabet Foot Ankle. 2012;3 https://doi.org/10.3402/dfa.v3i0.18809.
40. Assal M, Stern R. Realignment and extended fusion with use of a medial column screw for midfoot deformities secondary to diabetic neuropathy. J Bone Joint Surg Am. 2009;91:812–20.
41. Wirth SH, Viehofer AF, Tondelli T, Hartmann R, Berli MC, Böni T, et al. Mid-term walking ability after Charcot foot reconstruction using the Ilizarov ring fixator. Arch Orthop Trauma Surg. 2020;140(12):1909–17. https://doi.org/10.1007/s00402-020-03407-5.
42. Lipsky BA. Empirical therapy for diabetic foot infections: are there clinical clues to guide antibiotic selection? Clin Microbiol Infect. 2007;13:351–3.
43. Uçkay I, Pittet D, Vaudaux P, Sax H, Lew D, Waldvogel F. Foreign body infections due to *Staphylococcus epidermidis*. Ann Med. 2009;41:109–19.
44. Richard JL, Sotto A, Jourdan N, Combescure C, Vannereau D, Rodier M, et al. Risk factors and healing impact of multidrug-resistant bacteria in diabetic foot ulcers. Diabetes Metab. 2008;34:363–9.
45. Reber A, Moldovan A, Dunkel N, Emonet S, Rohner P, Tahintzi P, et al. Should the methicillin-resistant *Staphylococcus aureus* carriage status be used as a guide to treatment for skin and soft tissue infections? J Infect. 2012;64:513–9.
46. Uçkay I, Teterycz D, Ferry T, Harbarth S, Lübbeke A, Emonet S, et al. Poor utility of MRSA screening to predict staphylococcal species in orthopaedic implant infections. J Hosp Infect. 2009;73:89–91.
47. Gariani K, Lebowitz D, Kressmann B, von Dach E, Sendi P, Waibel F, et al. Oral amoxicillin-clavulanate

for treating diabetic foot infections. Diabetes Obes Metab. 2019;21:1483–6.
48. Schaper NC, Dryden M, Kujath P, Nathwani D, Arvis P, Reimnitz P, et al. Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study. Infection. 2013;41:175–86.
49. Lipsky BA, Armstrong DG, Citron DM, Tice AD, Morgenstern DE, Abramson MA. Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP): prospective, randomised, controlled, double-blinded, multicentre trial. Lancet. 2005;366:1695–703.
50. Lipsky BA, Stoutenburgh U. Daptomycin for treating infected diabetic foot ulcers: evidence from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic penicillins for complicated skin and skin-structure infections. J Antimicrob Chemother. 2005;55:240–5.
51. Nelson EA, O'Meara S, Golder S, Dalton J, Craig D, Iglesias C. Systematic review of antimicrobial treatments for diabetic foot ulcers. Diabet Med. 2006;23:348–59.
52. Embil JM, Rose G, Trepman E, Math MC, Duerksen F, Simonsen JN, et al. Oral antimicrobial therapy for diabetic foot osteomyelitis. Foot Ankle Int. 2006;27:771–9.
53. Spellberg B, Lipsky BA. Systemic antibiotic therapy for chronic osteomyelitis in adults. Clin Infect Dis. 2012;54:393–407.
54. Waibel F, Berli M, Catanzaro S, Sairanen K, Schoni M, Boni T, et al. Optimization of the antibiotic management of diabetic foot infections: protocol for two randomized controlled trials. Trials. 2020;21:54.
55. Lipsky BA, Berendt AR, Cornia PB, Pile JC, Peters EJ, Armstrong DG, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2012;54:132–73.
56. Tobalem M, Uçkay I. Evolution of a diabetic foot infection. New Engl J Med. 2013;369:2252.
57. Dworkin MS, Westercamp MD, Park L, McIntyre A. The epidemiology of necrotizing fasciitis including factors associated with death and amputation. Epidemiol Infect. 2009;137:1609–14.
58. Lazzarini L, Lipsky BA, Mader JT. Antibiotic treatment of osteomyelitis: what have we learned from 30 years of clinical trials? Int J Infect Dis. 2005;9:127–38.
59. Gariani K, Lebowitz D, von Dach E, Kressmann B, Lipsky BA, Uçkay I. Remission in diabetic foot infections: duration of antibiotic therapy and other possible associated factors. Diabetes Obes Metab. 2019;21:244–51.
60. Tone A, Nguyen S, Devemy F, Topolinski H, Valette M, Cazaubiel M, et al. Six-week versus twelve-week antibiotic therapy for nonsurgically treated diabetic foot osteomyelitis: a multicenter open-label controlled randomized study. Diabetes Care. 2015;38:302–7.
61. Lebowitz D, Gariani K, Kressmann B, Dach EV, Huttner B, Bartolone P, et al. Are antibiotic-resistant pathogens more common in subsequent episodes of diabetic foot infection? Int J Infect Dis. 2017;59:61–4.
62. Simpson AH, Deakin M, Latham JM. Chronic osteomyelitis. The effect of the extent of surgical resection on infection-free survival. J Bone Joint Surg Br. 2001;83:403–7.
63. Pittet D, Wyssa B, Herter-Clavel C, Kursteiner K, Vaucher J, Lew PD. Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up. Arch Intern Med. 1999;159:851–6.
64. Jeffcoate WJ, Lipsky BA. Controversies in diagnosing and managing osteomyelitis of the foot in diabetes. Clin Infect Dis. 2004;39:115–22.
65. Uçkay I, Kressmann B, Malacarne S, Toumanova A, Jaafar J, Lew D, et al. A randomized, controlled study to investigate the efficacy and safety of a topical gentamicin-collagen sponge in combination with systemic antibiotic therapy in diabetic patients with a moderate or severe foot ulcer infection. BMC Infect Dis. 2018;18:361.
66. Dunkel N, Pittet D, Tovmirzaeva L, Suvà D, Bernard L, Lew D, et al. Short duration of antibiotic prophylaxis in open fractures does not enhance risk of subsequent infection. Bone Joint J. 2013;95-B:831–7.
67. Bernard L, Legout L, Zürcher-Pfund L, Stern R, Rohner P, Peter R, et al. Six weeks of antibiotic treatment is sufficient following surgery for septic arthroplasty. J Infect. 2010;61:125–32.
68. Jugun K, Richard JC, Lipsky BA, Kressmann B, Pittet-Cuenod B, Suvà D, et al. Factors associated with treatment failure of infected pressure sores. Ann Surg. 2016;264:399–403.
69. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE, Weibel S. Hyperbaric oxygen therapy for chronic wounds. Cochrane Database Syst Rev. 2015;2015:004123.