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Review

Diabetic foot infections: what have we learned in the last 30 years?

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SUMMARY

Background: Infection is a common epiphenomenon of advanced diabetic foot disease and the most common reason for diabetes-related hospitalizations and lower extremity amputations. Major advances have been made in the past three decades in our understanding and management of diabetic foot infections (DFIs). The optimal treatment of DFIs clearly involves multidisciplinary input.
Methods: A comprehensive search of the literature on DFIs from January 1960 through June 2015 was performed, with an emphasis on information published in the past 30 years.
Results: There have been many new insights into the microbiology, diagnosis, and treatment of DFIs, although the implementation of this knowledge in clinical practice has been suboptimal. Today, the use of 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. New diagnostic and therapeutic methods are being developed at an accelerating pace.
Conclusions: The worldwide increase in the incidence of diabetes and longer lifespan of diabetic patients will undoubtedly increase the incidence of DFIs. Clinicians caring for diabetic patients should have an understanding of current methods for preventing, diagnosing, and treating DFIs.

1. Introduction

The incidence of foot infections in persons with diabetes ranges from a lifetime risk of up to 25% in all persons with the diagnosis, to 4% yearly in patients treated in a diabetic foot center.[1] Diabetic foot infections (DFIs) occasionally present as cellulitis or post-traumatic (including postsurgical) infections,[2] but are most commonly a consequence of ulcerations secondary to progressive peripheral polyneuropathy. This causes a loss of protective sensation, as well as foot deformities, gait disorders, anterior displacement of weight-bearing during walking,[3] and reduced mobility. These neurological problems are commonly accompanied by arterial insufficiency and immunological disturbances. Developing a DFI is now the most common diabetes-related reason for hospitalization and lower extremity amputation.[4] This review aims to review the growth of knowledge over the past 30 years on the pathogens,[5,6] radiological diagnosis,[7] and medical[8,9,10] and surgical treatments of DFI.[11]

2. Management of diabetic foot infections: 1985 and 2015

Few of today's clinicians appreciate how limited were the knowledge base and therapeutic arsenal available to manage DFI 30 years ago. Although the problem was common, there were remarkably few scientific papers published on DFIs. The major source of clinical information was textbooks, the most comprehensive of which was *The Diabetic Foot*. The chapter on infection in the first edition, published in 1973, emphasized the importance of vascular insufficiency and gangrene, with little discussion of treatment, and none of the references were specifically on DFI.[12] The third edition (1983) was the first with a DFI reference,[13] and it was not until the fourth edition (1988) that there was a discussion of wound culture techniques.[14] In the mid 1980s, the general belief was that (1) the major pathophysiological cause of DFIs was limb

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ischemia (especially small vessel disease), leading to gangrene; (2) DFIs were almost always polymicrobial, with obligate anaerobes playing a major role; (3) nearly all patients with a DFI should be hospitalized and treated with broad-spectrum parenteral antibiotic therapy; and (4) severe or apparently non-responsive infections usually required a lower extremity amputation. We now know that virtually all of these concepts were wrong. While the prevalence of diabetic foot disease (especially as a cause of hospitalization) has increased, ulcers and infection, not vascular disease, are now the major underlying cause (Figures 1 and 2).

Progress in the understanding of diabetic foot problems accelerated with the first (of what are now many) diabetic foot meeting, held in Malvern, UK in 1986. In 1987 the American Diabetes Association (ADA) started a Foot Council, which held a symposium at their annual meetings. In 1991 the International Working Group on the Diabetic Foot (IWGDF) held the first of its quadrennial meetings, and the European Association for the Study of Diabetes founded a Diabetic Foot Study Group (with an annual meeting) in 1998.

These scientific organizations and meetings helped trigger a dramatic increase in the number of publications (and citations) on DFIs (Figures 3 and 4). The growth of scientific evidence allowed various organizations to produce guidelines for diabetic foot care, beginning with those of the ADA and IWGDF in the late 1990s. One of the major achievements in the last 30 years was the recognition of the value of a multidisciplinary approach to this complex problem,[15] which led to the opening of specialized diabetic foot centres all over the world. Unfortunately, the implementation and translation of this knowledge into therapeutic success has been more limited. While some centres have improved various parameters of DFI care, many, especially in resource-poor countries, have not. Table 1 summarizes the authors' views on the major changes in our understanding of, and approach to, DFIs since 1985.

3. International recommendations, guidelines, and classifications

There has been a proliferation of guidelines, checklists, and classification schemes regarding DFIs in the last 30 years. The first guidelines specifically devoted to DFI, both published in 2004, were those commissioned by the Infectious Diseases Society of America (IDSA) and by the IWGDF. These have been updated,[16–18] and we refer readers interested in the literature regarding definitions, classifications, differential diagnoses of infection,[19] and guidelines to other literature to our prior publications.[8,20]

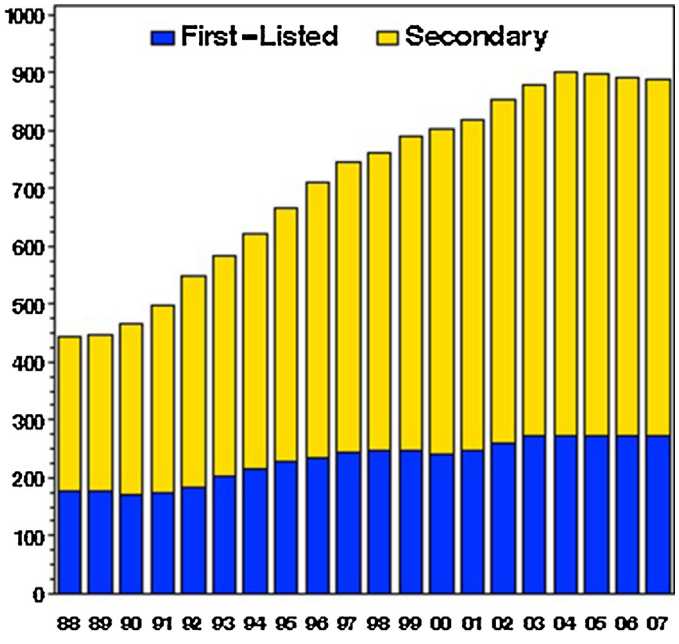

Figure 1. Number of hospital discharges, by year, for diabetes-related lower extremity conditions (in thousands), USA, 1988–2007 (http://www.cdc.gov/diabetes/statistics, accessed 30 June 2015).

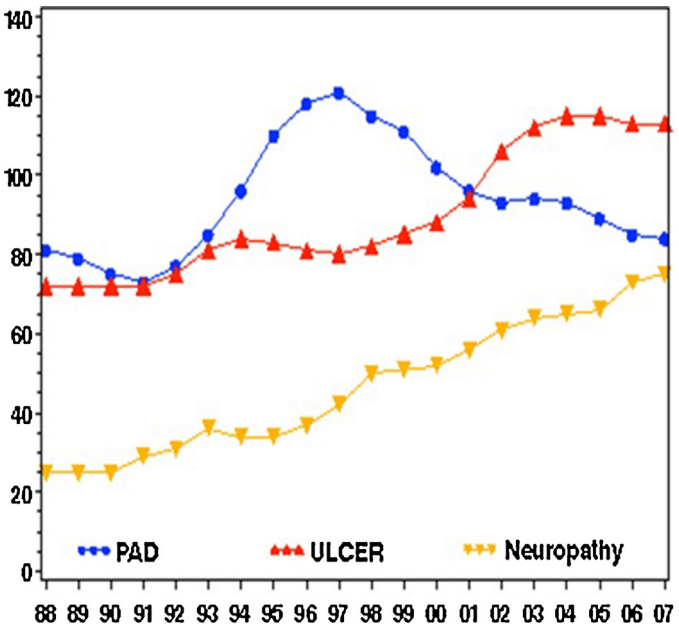

Figure 2. Major causes of hospital discharge, by year, for diabetes-related lower extremity conditions (in thousands), USA, 1988–2007 (http://www.cdc.gov/diabetes/statistics, accessed 30 June 2015).

4. Pathogens

Starting in the late 1970s, studies demonstrated that aerobic Gram-positive cocci (especially *Staphylococcus aureus*), often as monomicrobial infections, were the predominant pathogens in DFIs, with aerobic Gram-negative rods found mostly in patients

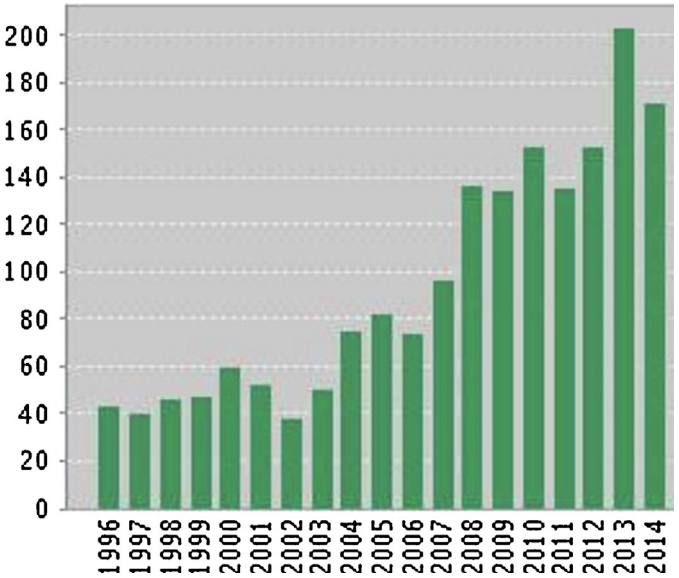

Figure 3. Published items per year located with the search term "diabetic foot infection" in Web of Science.

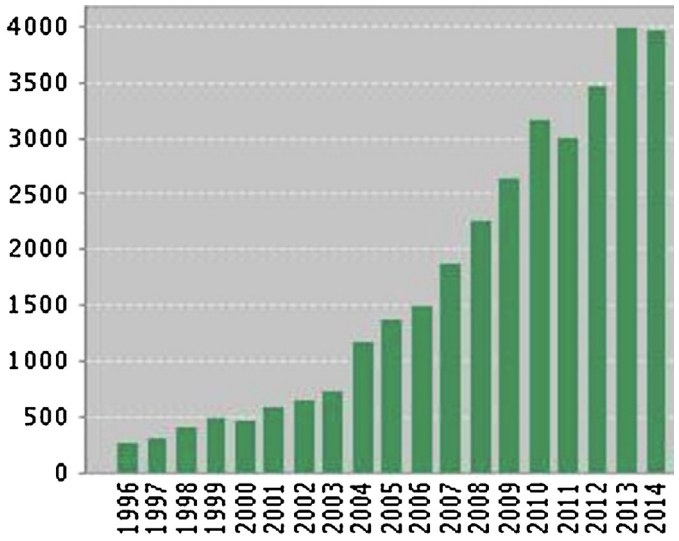

Figure 4. Number of citations per year for published papers located with the search term "diabetic foot infection" in Web of Science.

with chronic, previously treated wounds. In recent years DFIs caused by multidrug-resistant organisms, such as extended-spectrum beta-lactamase-producing Gram-negative rods[21] or methicillin-resistant *S. aureus* (MRSA), have emerged as a substantial problem. Infection with an antibiotic-resistant organism certainly requires the selection of an agent active against that isolate, but should not otherwise alter therapeutic management.[22] Studies of outcomes of DFIs caused by multi-resistant pathogens compared with other organisms have produced conflicting results, with some finding no worse outcomes,[23,24] while others have.[25] In a previous study, we found that among 48 papers published between 1999 and 2013, only five attempted a comparison of outcomes between DFIs caused by MRSA and those caused by other pathogens.[5] Overall, there were no clear differences in outcomes, but many trials failed to adjust for case-mix, or to seek a relationship between microbiology and outcomes. Notwithstanding the limitations of the available literature, we do not believe there is a need for any special treatment (other than selecting an active antibiotic agent) for DFIs caused by MRSA.[5]

Until the most recent decade, the majority of studies on the microbiology of DFI were conducted in North America and Europe. In recent years, investigations in warm climates (especially India, but also the Middle East and Africa) have found the most common isolates to be Gram-negative rods, particularly *Pseudomonas aeruginosa*. We can only speculate on the reasons for this disparity, but they may include a hot climate causing foot sweating, the use of poor footwear, a high incidence of patient self-treatment with antimicrobials, frequent foot washing, and suboptimal perineal/hand hygiene.[8] Thus, clinicians in these regions should consider covering *Enterobacteriaceae* and *Pseudomonas spp*, pending culture and sensitivity results.

When treating DFIs, clinicians have frequently added antibiotic agents that are specifically directed against obligate anaerobic bacteria, especially when the wound is gangrenous or has a fetid odour. However, our recent literature review of DFI studies revealed that anaerobes were infrequent isolates, were not associated with any specific clinical findings, and did not clearly lead to more severe manifestations.[6] *Bacteroides* and *Peptostreptococcus* have been the two main species reported, but it is uncertain if they are pathogens or colonizers associated with the presence of a greater degree of tissue ischemia or necrosis. Most clinical trials of antimicrobial therapy for DFI have not employed adequate methods to culture anaerobic organisms. One randomized trial

Table 1
Key changes in the knowledge and management of diabetic foot infections in the last 30 years—summary of the authors' views

Research field	1985	2015
Pathogens	Methicillin-susceptible *Staphylococcus aureus*, streptococci, *Enterobacteriaceae*	More multidrug-resistant organisms (MRSA, ESBLs) Predominance of Gram-negative pathogens in (sub)tropical climates
Microbiological diagnosis	Standard cultures, usually of swab specimens	Aerobic and anaerobic cultures of tissue specimens (soft tissue and bone) Molecular microbiology (e.g., PCR) Metagenomics
Imaging	Plain X-rays; scintigraphy (bone, leukocyte scans)	MRI; SPECT/CT; PET/CT
Antibiotic agents	Penicillins; 1st to 3rd generation cephalosporins; some 2nd generation fluoroquinolones	4th/5th generation cephalosporins; carbapenems; 3rd/4th generation fluoroquinolones; linezolid; daptomycin
Route of administration and site of treatment	Initial (sometimes prolonged) intravenous administration, usually in hospital	Mostly oral (sometimes after a brief intravenous course), even in the presence of vascular disease or osteomyelitis; some topical; outpatient except for severe infections or complex treatments
Spectrum of antibiotic therapy	Relatively broad (directed at Gram-positive and Gram-negative pathogens)	Very broad empiric therapy for severe infections; more targeted for mild/moderate infections and for definitive therapy
Duration of antibiotic therapy	Many weeks for soft tissue infections; ≥6–12 weeks for bone	1–2 weeks for soft tissue infections; 4–6 weeks for osteomyelitis
Surgical approach	Aggressive (ablative) therapeutic surgery; inpatient treatment	More conservative (tissue sparing) therapeutic (even for osteomyelitis) and preventive surgery; corrective surgery; often in outpatient facilities and specialized diabetic foot centres
Revascularization	Open vascular surgery	More percutaneous angioplasty and distal bypasses, including infragenicular
Management	Mostly individual, empirical approaches	Clinical guidelines based on systematic reviews; multidisciplinary teams, especially including podiatry; clinical pathways; some behavioural sciences
guidelines	Individual recommendations and practices on the hospital level	national guidelines; validation of guidelines
Adjunctive treatments	Stimulation with growth factors; platelet-rich products; larval biotherapy (maggots)	Hyperbaric oxygen therapy; granulocyte-stimulating factors; research in stem cell and bacteriophage therapies; microbiome concepts
Dressing	Simple dressings, with separate use of disinfection agents	More hydrofibre and silver-containing dressings; studies with topical antibiotics embedded in dressings
Scientific publications	Mostly case series	More prospective randomized trials, multicenter studies, and evidence-based (Cochrane) meta-analyses

ESBL, extended-spectrum beta-lactamase; MRI, magnetic resonance imaging; MRSA, methicillin-resistant *Staphylococcus aureus*; PET/CT, positron emission tomography/computed tomography; SPECT/CT, single photon emission computed tomography/computed tomography.

optimized for the isolation of anaerobic pathogens reported that among six groups (i.e., Gram-positive anaerobic cocci, *Peptostreptococcus magnus*, *Peptostreptococcus asaccharolyticus*, Gram-positive anaerobic bacilli, Gram-negative anaerobic bacilli, and Gram-negative anaerobic coccobacilli, including here *Bacteroides spp*), none was associated with worse outcomes.[26] Several randomized trials of DFIs, including soft tissue or osteomyelitis cases, have reported similar clinical success rates when comparing regimens with similar anaerobic spectra,[27,28] and equivalent outcomes with drugs that have broad anaerobic coverage compared to those with a narrower spectrum.[29–31] Finally, local mycobacterial infections or tetanus are rare causes of DFI.[32]

4.1. Microbiome and metagenomics

Standard culture methods, which have changed little in 150 years, are limited by taking several days to complete, being falsely negative in patients receiving antibiotic therapy, and failing to identify many fastidious bacteria. Newer molecular techniques, such as 16S PCR and gene sequencing, typically identify a greater number and variety of bacteria, particularly anaerobes.[33] Metagenomic studies have revealed interplay among bacterial communities in various environments, including wounds, that produce specific clinical 'syndromes'[33–35] or phenotypic diseases. This recent and rapidly emerging research area may provide more insights into the potential association of the skin (and gastrointestinal) microbiome with DFI.[33]

5. Treatment

5.1. Podiatric care

Most patients with a DFI require some form of podiatric care, along with medical, surgical, nursing, and physiotherapeutic interventions.[20] The increasing availability of podiatrists in many countries appears to have led to major advances in diabetic foot care, although robust evidence for this is pending.[36] Podiatric care is particularly aimed at preventing foot complications and includes debridement of callus[37] and necrotic tissue, nail care (especially with onychomycosis), the treatment of blisters, prescribing proper footwear, and fitting orthotic devices. Once complications occur, however, the goal becomes avoiding amputation.

5.2. Systemic antimicrobial therapy

Systemic antibiotic therapy is always necessary for the treatment of clinically infected wounds, but is often insufficient to cure moderate to severe DFIs.[16] This systemic therapy must often be combined with one or more surgical procedures, pressure off-loading, appropriate wound care, and in some cases, arterial revascularization. With a few exceptions,[38] almost all of the currently used antimicrobial classes (if not the current generations) were available 30 years ago. What has changed is our awareness of the need to reduce the spectrum and duration of antibiotherapy to try to slow the tide of antibiotic resistance. While initial antibiotic therapy for most patients must be selected empirically, it should largely be based on the assessment of infection severity[12] and knowledge of the local microbial epidemiology. In most regions of the world, the antibiotic regimen should always cover *S. aureus*, but it may be broadened to include Gram-negative isolates in severe infections or if the patient has failed to respond to prior narrower-spectrum therapy. Of note, DFIs can develop rapidly,[39] making early follow-up after starting therapy imperative. Necrotizing soft tissue infections of the diabetic foot, including gas gangrene, are uncommon and are usually caused by mixed aerobic (and sometimes anaerobic) bacteria rather than *Clostridium* species.[40]

Definitive antibiotic therapy should be based on culture and sensitivity results. Even if cultures yield multiple organisms, it may be sufficient to treat only the likeliest pathogens, such as *S. aureus*, streptococci, and *Enterobacteriaceae*. Skin commensals such as coagulase-negative staphylococci, corynebacteria, or *Bacillus spp*, and low-virulence organisms such as enterococci, can usually be ignored unless cultured from deep, aseptically collected tissue or infections involving osteosynthetic material or hardware. Likewise, the mere presence of skin or mucosal colonization with healthcare-associated MRSA does not oblige the clinician to empirically cover this organism,[40,41] even in the presence of underlying osteosynthetic material.[42] Quantitative cultures, which were in vogue in the past, are now rarely done as they are difficult to perform, expensive, and do not add much to deciding which wounds are infected or what organisms to treat.[35,43,44]

Because most DFIs occur in the setting of peripheral arterial disease, some have raised concerns about how well various antibiotic agents penetrate the infected site, especially bone. This has led many clinicians to prescribe weeks of intravenous antibiotic therapy. The current availability of highly bioavailable oral antibiotics, as well as the acquisition of further evidence of the efficacy of oral antibiotic regimens, has helped change this practice. When prescribed at standard doses, most beta-lactam antibiotics achieve relatively low (albeit therapeutic) tissue levels, as these are time-dependent (not concentration-dependent) drugs. Clindamycin, fluoroquinolones, linezolid, rifampicin, and to some degree, tetracyclines and co-trimoxazole, have good oral bioavailability and penetration in bone, synovia, biofilm, and necrotic tissue.[8] Few data support the need for parenteral therapy,[45] and studies are currently underway to compare outcomes of oral versus intravenous therapy for complex musculoskeletal infections, including DFI. Likewise, in a retrospective analysis of more than 2000 episodes of orthopaedic infection, including DFI, we found no evidence of superiority of bactericidal agents over bacteriostatic agents.[46] Similarly, published randomized controlled DFI trials have failed to show superiority of any particular antibiotic agent or route of administration.[8] Several systematic reviews of antimicrobial treatments for DFI have concluded that there is insufficient evidence to recommend any particular antimicrobial agent or route of administration.[47–49]

5.3. Osteomyelitis: diagnosis and therapy

DFIs generally begin when a break in the protective skin barrier allows pathogens to multiply in the soft tissues. Diabetic foot osteomyelitis usually occurs by the contiguous spread of infection from overlying soft tissue. Osteomyelitis is found in up to 15% of patients with a clinically uninfected diabetic foot ulcer; among those with a DFI, however, approximately 20% seen in the outpatient setting and two-thirds who are hospitalized have infected bone at presentation.[8] Diagnosing osteomyelitis of the diabetic foot can be difficult, especially early in the course. Clinical findings suggesting infection include a deep chronic ulcer over a bony prominence, 'sausage toe' (red, warm, swollen) appearance, and an erythrocyte sedimentation rate >70 mm/h. The only virtually pathognomonic clinical sign is the presence of fragments of bone discharging from a wound. The probe-to-bone test is helpful in diagnosing diabetic foot osteomyelitis if it is correctly performed (with a blunt metal probe) and interpreted (with consideration of the pre-test probability of osteomyelitis). Based on several reports, the sensitivity ranges from about 60% to 87%, specificity from 85% to 91%, and positive predictive value from 87% to 90%, but the negative predictive value is only 56–62%.[50–52] The criterion standard for diagnosing osteomyelitis remains a culture

of bone and, when possible, histopathological examination.[53] Recent prospective trials have shown that culture results of soft tissue or of needle puncture specimens of bone often fail to correlate with transcutaneous or operative bone specimens,[54] and non-invasive diagnostic approaches for the microbiological assessment of toe osteomyelitis should probably be abandoned.[55]

5.3.1. Radiological assessment of osteomyelitis

As in the past, imaging tests should generally begin with plain X-rays. We now know that inter-observer reproducibility is poor, especially among inexperienced clinicians,[56] and early osteomyelitis may be missed because it takes several weeks for bone lesions to become radiologically detectable. When plain X-rays are inconclusive, or when more detail of bone or soft tissue abnormalities is required, magnetic resonance imaging (MRI) is superior to the standard radionuclide studies (which have lower specificities). Meta-analyses of the performance of three-phase bone scintigraphy for detecting DFI using only planar imaging, or combined with single photon emission computed tomography (SPECT), report sensitivity of approximately 90%, but specificity of only approximately 50%.[7] Newer hybrid imaging techniques (SPECT/CT, positron emission tomography (PET)/CT, and PET/MRI) look to be useful, and improved radiopharmaceuticals are on the horizon.[7]

5.3.2. Treatment of osteomyelitis

The past decade has provided much new information on how to treat diabetic foot osteomyelitis. One study of 50 patients with chronic toe osteomyelitis reported that patients who underwent wide surgical resection had a significantly lower relapse rate than those who underwent less aggressive surgery.[57] Contrary to the teaching of 30 years ago, there are now reports of hundreds of cases of diabetic foot osteomyelitis treated without surgery, with remission rates of 60% to 70%;[58,59] one recent randomized controlled trial showed similar cure rates for medical and for primarily surgical therapy.[60] Thus, when the patient or the medical team prefers to avoid surgery, a trial of exclusively antibiotic therapy may be reasonable. Regarding the duration of antibiotic therapy, a systematic review of the treatment of osteomyelitis in patients with and without diabetes found that there was no evidence that antibiotic therapy for more than 4–6 weeks improves outcomes compared with this duration.[61] More recently, a small randomized controlled study found that 6 weeks compared with 12 weeks of antibiotic treatment of diabetic foot osteomyelitis produced similar results.[62]

5.4. Topical antibiotics, antiseptic disinfectants, and peptides

Superficial, open wounds without extensive cellulitis can potentially be treated with topical antimicrobials.[9] The few published studies of topical therapy for DFI have employed a variety of antibiotics (e.g., mupirocin, bacitracin, neomycin, chloramphenicol, polymyxin B, and gentamicin), as well as antiseptics.[9,63] We found no publication reporting on the use of topical fusidic acid for DFI, an agent often misused in other types of superficial skin infection in many parts of the world.[9] Studies of topical therapy comparing an active agent to a placebo, to another active agent, or as adjuncts to systemic antibiotic therapy, have provided mixed results.[64] In DFI, topical agents are typically applied in mildly infected (or, inappropriately, in uninfected) wounds, making it difficult to distinguish their clinical benefits from local wound care alone. Just eradicating or reducing microorganisms in the wound is not a sufficient endpoint for efficacy,[65] any more than their presence is sufficient to define clinical infection. There is no evidence that topical (or systemic) antimicrobial therapy hastens healing of uninfected wounds, or that it prevents clinically apparent wound infection.[66,67] A pilot randomized study of treatment in 56 DFI patients found that adding a topical gentamicin-collagen sponge as an adjunct to systemic antibiotic therapy (for up to 28 days), produced a higher infection cure rate compared to systemic antibiotics alone (100% vs. 70%, respectively) at 2 weeks after the end of therapy.[63] In another randomized trial, adding a gentamicin-collagen sponge to systemic antibiotic therapy after a minor foot amputation in 50 patients resulted in a significantly shorter (by almost 2 weeks) median stump wound healing time.[67] The largest study of topical antimicrobial therapy in patients with a DFI (with 835 evaluable patients) found that treatment with an investigational antimicrobial peptide cream (pexiganan) produced rates of clinical cure, pathogen eradication, and wound healing similar to those in patients treated with an oral fluoroquinolone antibiotic (ofloxacin).[68] Further studies of this agent in treating mild DFI are currently underway.

Many studies have assessed topical disinfectants or antiseptics for the treatment of DFI, including compounds with silver,[69] povidone or cadexomer iodine, or hypochlorite. 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.[8] Likewise, recent systematic reviews have found that various other dressings, such as foam,[70,71] hydrocolloid,[72] or alginate,[73] offer no advantage over other dressings for ulcer healing or resolution of infection.[8] Thus, as was true three decades ago, dressing changes with simple gauze and saline solution alone appears to be sufficient for most patients.

5.5. Antibiotic misuse

Excessive and inappropriate uses of antibiotics have profound negative effects, firstly for the patient, but also for the health care system and society as a whole.[9] Diabetic foot experts,[74,75] including the authors of the most recent IDSA[16] and IWGDF[18] guidelines on DFI, the European Wound Management Association policy document,[65] and the Scottish consensus statement,[76] recommend not treating clinically uninfected ulcers with antibiotic therapy. One double-blind, placebo-controlled trial in which 39 patients with an 'uncomplicated' neuropathic diabetic foot ulcer were treated with either antibiotic therapy (oral amoxicillin–clavulanate) or placebo found no difference in the wound healing rates.[77] Similarly, a study of patients with neuropathic (presumably uninfected) foot ulcers found no significant difference in ulcer healing for 25 patients treated with parenteral antibiotic therapy (ceftriaxone) compared to 25 controls not treated with antibiotics.[78] A large registry study in Sweden showed that providing web-based information on appropriate ulcer care was associated with a highly significant reduction in antibiotic prescribing for these wounds, from 71% to 29%.[79] This finding not only supports the premise that antibiotics are not necessary in the majority of ulcers (presumably those that are uninfected) treated with appropriate wound care, but also that it is possible to improve antibiotic prescribing by clinicians.

5.6. Surgery

Surgery undoubtedly plays an important role in the treatment of many types of DFI (see Figures 5–7),[80–82] but until recently there has been limited evidence regarding what constitutes optimal surgical treatment.[83] The major aims of surgery in DFIs are to evacuate pus, remove necrotic tissue, and minimize the risk of further spread.[80,84] Bad outcomes are often related to a delayed diagnosis, leading to extensive destruction of the soft tissue.[85] Despite a strong emphasis in recent guidelines and consensus

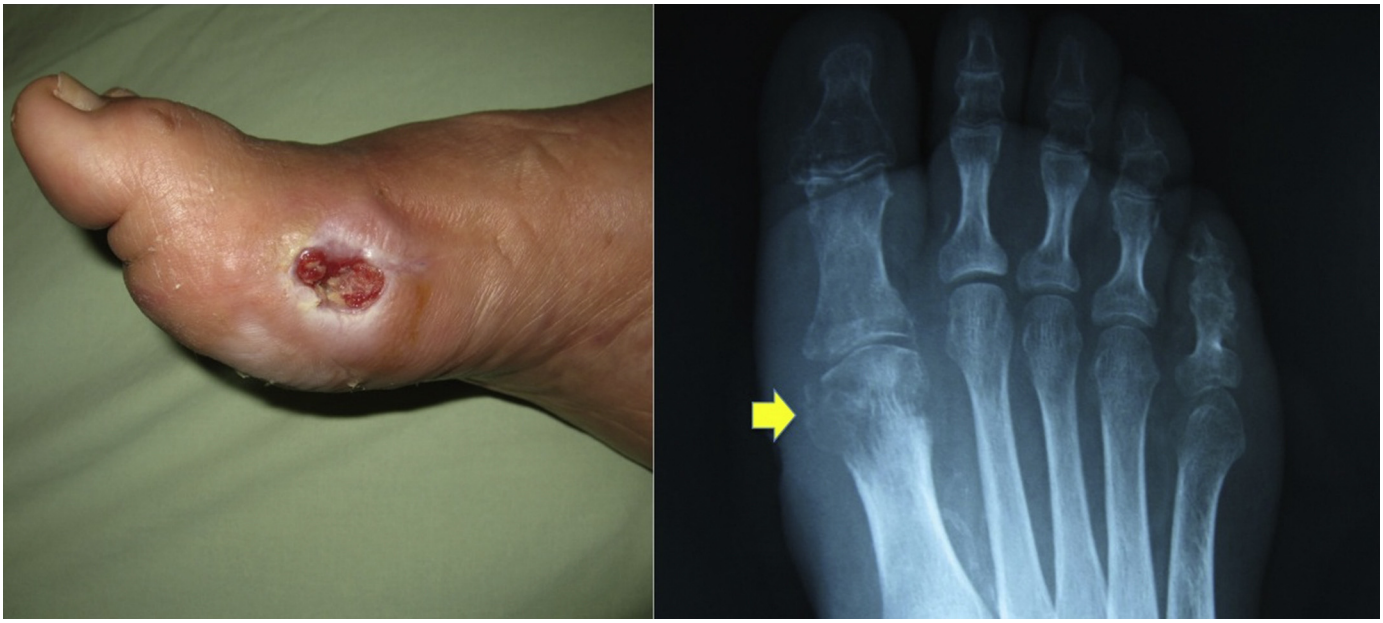

Figure 5. Ulcer over the first metatarsal head: X-ray showing cortical destruction of the first metatarsal head.

documents on the importance of prompt surgical intervention in many DFIs, it is frequently delayed, sometimes leading to amputation.[86,87] More conservative surgery for the treatment of DFIs is now possible because we better understand the compartmental anatomy of the foot and the ways in which infection spreads.[88,89] Furthermore, it is clear that there are more types of foot infection than just 'abscesses' and 'diabetic gangrene'.[90] We now also appreciate that combining needed ablative foot surgery with prompt revascularization can improve the rate of limb salvage.[91] And, finally, new wound therapies have improved the postoperative care for these patients.[92]

Any foot compartment affected by infection should be opened quickly to reduce the compartmental pressure.[93] Contrary to previously held beliefs, fascial planes do not constrain the spread of infection.[94] Although unproven, MRI may play a role in planning the surgical approach.[85,95] Unfortunately, there is no classification that defines either the point at which surgery is absolutely necessary, or when it is likely to produce a better outcome than further medical therapy.[96–98] It is now clear, however, that in most cases 'conservative' surgery (i.e., resection of just the affected bone, without amputation)[96,99–101] or antibiotic therapy alone can treat osteomyelitis successfully.

The optimal timing of surgery for DFI is not well defined, but prompt surgery, including revascularization when necessary, may reduce the need for above-ankle amputations.[102–104] The rate of success, including avoiding lower extremity amputation, in DFIs, depends on the approach taken by the treating surgeon,[105] which often reflects his or her experience and skills. When amputation is

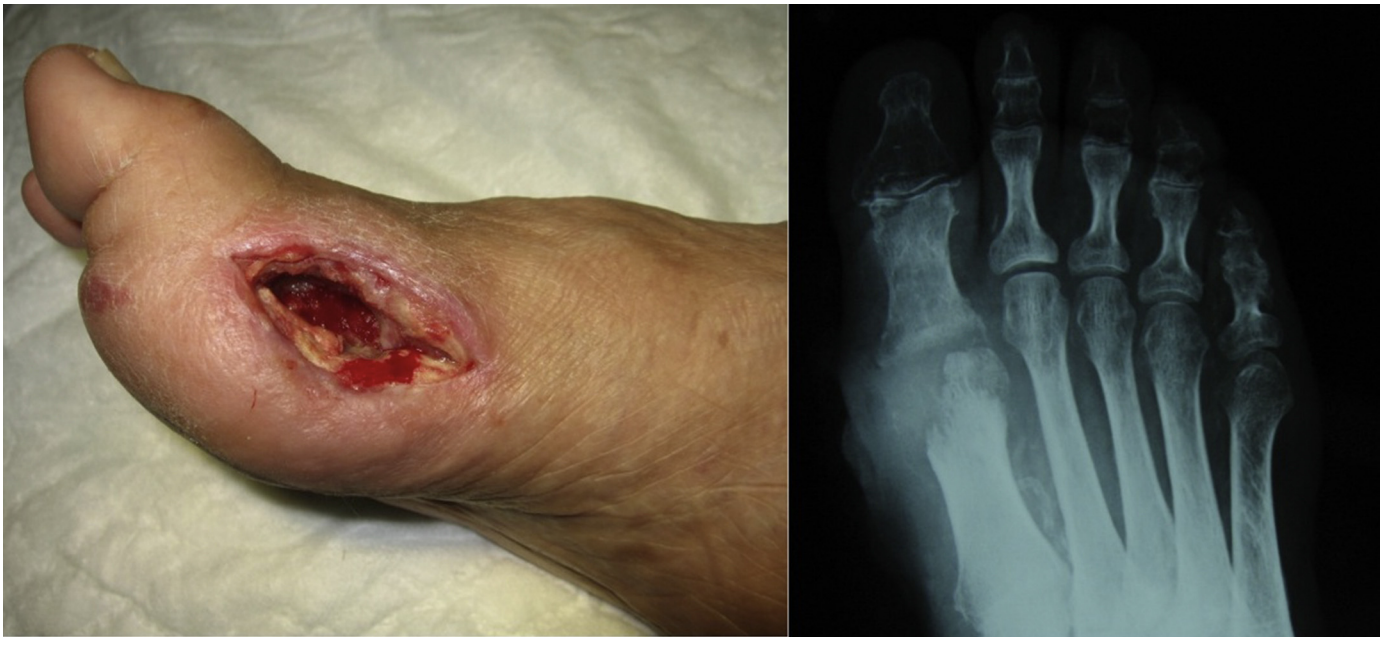

Figure 6. Postoperative view: X-ray showing the bone that was removed.

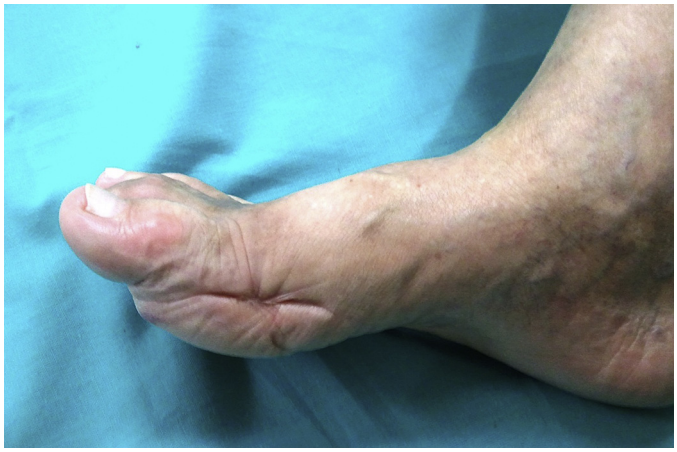

Figure 7. Total healing of the wound.

performed, both the vertical level of the limb/foot and the horizontal anatomical involvement help determine wound healing. In a recent study of diabetic foot osteomyelitis cases that were treated surgically, those involving the first metatarsal joint were less likely to heal than those in other locations, such as the lesser toes.[106] For patients with wet gangrene or sepsis, a two-stage amputation (initial guillotine with later revision) may lead to better primary stump healing than a one-stage procedure.[107] Contrary to previous beliefs, soft tissue coverage by skin grafting or flaps is possible if needed, even in ischemic areas.[108]

6. Negative-pressure wound therapy

We now have wound healing devices that were not even dreamed of 30 years ago. Negative-pressure wound therapy (NPWT), introduced about 20 years ago, is now widely used for accelerating wound healing. There are, however, few published data on the usefulness of this method for treating infected soft tissue or bone.[109] A systematic review identified four randomized trials of NPWT for diabetic foot wounds.[110] While all, including a multicenter study that enrolled 342 patients,[111] found that wounds treated with NPWT healed more rapidly than those receiving conventional dressings, the quality of each of the studies was weak and there was heterogeneity in the outcomes studied and patients selected.[112,113] A more recent meta-analysis of four randomized trials in diabetic foot ulcers concluded that NPWT results in more effective and faster wound healing and may reduce potential infective complications.[113] A Cochrane review identified two large trials that reported superior ulcer healing results with NPWT compared to moist dressing alone, but three other smaller trials did not confirm this finding. None of these trials dealt with infection.[114] NPWT can be combined with simultaneous wound irrigation or the instillation of antiseptics or antibiotics to reduce the 'wound bed bioburden,' but the effectiveness of these methods for curing or preventing infection is as yet unclear.[115] One case–control study including 82 diabetic patients demonstrated a significantly shorter length of hospital stay and a reduced number of surgical visits in patients treated with negative pressure therapy with antimicrobial installation compared to negative pressure therapy without installation.[116] More trials are needed to better understand what role this instillation technique may have in treating DFI.

7. Off-loading

Off-loading pressure from an ulcer is critical to getting it to heal, including those that are infected.[117] 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.[117] What is new is recognizing that the key to its success is that it is non-removable, ensuring patient adherence.[118] For patients with little or no foot deformity, prefabricated extra depth footwear with a stiff rocker bottom walking sole is usually sufficient. Cases with a moderate deformity may require custom-made shoes with custom-moulded, 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.[119]

Clinicians should generally explain to the patient the benefit of off-loading, but a recent Cochrane analysis of patient education for preventing diabetic foot ulcers found that it may positively influence short-term results, but overall there is still insufficiently robust evidence that limited education alone is effective in achieving a significant reduction in the incidence of foot ulceration and amputation.[120,121]

8. Adjunctive treatments

8.1. Hyperbaric oxygen therapy

The value of hyperbaric oxygen therapy (HBOT) for DFI continues to be hotly debated.[8] 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.[122] 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,[123,124] but most experience is retrospective and non-comparative.[125] There are, however, no published data directly related to the effect of HBOT on infectious aspects (either soft tissue or bone) of the diabetic foot.[126]

8.2. Wound stimulating factors

Several studies have examined the value of granulocyte-colony stimulating factors for treating DFI or ulcers. A Cochrane review based on five randomized trials concluded that these treatments did not increase infection remission, but may reduce the need for surgical interventions, especially amputations, and the duration of hospitalization.[127] Well-designed studies of platelet-derived growth factors[128,129] and skin substitutes have not shown any specific benefit regarding resolution or prevention of infection.[130] Likewise, a Cochrane review found no evidence of benefit for autologous platelet-rich plasma in the treatment of chronic wounds.[131]

8.3. Stem cell therapy

In recent years there has been less research using growth factors on diabetic foot wounds and more employing stem cells.[132] Most of the initial studies used angiogenic growth factors alone, but the limited efficacy prompted studies investigating the potential benefits of cell-based therapy.[133,134] Studies on the local injection of unselected bone marrow-derived (or peripheral blood-derived) mononuclear cells in patients with severe peripheral arterial disease provided encouraging results, but the treatment did not provide complete revascularization, probably due to the limited delivery of specific angiogenic cells in the mixed cell population.[135] Later studies found that autologous bone marrow cell transplantation in ischemic diabetic foot ulcers increased leg perfusion and reduced

the risk of amputations.[136] Studies using umbilical cord stem cells have also reported encouraging results.[136] One investigation of adipose tissue-derived stem cell implantation in patients with critical limb ischemia, some of whom were diabetic, demonstrated considerable angioneogenesis.[137] Other investigators have also successfully harvested adipose tissue stem cells from the abdominal subcutaneous fat.[138] While stem cell therapy shows encouraging results regarding angiogenesis, it currently has no proven direct effect on infection.

9. Limb revascularization

Peripheral arterial disease is present in about 50% of patients with a DFI, and it appears to be an independent risk factor for limb loss.[139] Revascularization of the foot in diabetic patients can now be accomplished by either arterial bypass surgery or endovascular interventions, with limited evidence to support selecting one technique over the other. Available data suggest that patients with a life-expectancy of more than 2 years and extensive stenoses have superior outcomes with open surgery.[140] However, using endovascular angioplasty can reach the infragenicular region, which was not possible until the most recent decade.[141] While revascularization may be crucial for a critically ischemic limb, it probably has no directly beneficial effect on infection, other than to provide adequate perfusion to ensure the delivery of systemically administered antibiotics.

10. Clinical pathways, guidelines, and bundle interventions

As noted above, there are now several evidence-based DFI guidelines that have been shown to provide validated approaches to optimize outcomes.[20] All address the critical importance of multidisciplinary teams,[16] which have repeatedly been shown to help avoid adverse outcomes in both inpatients and outpatients with DFIs.[142] The deployment of teams is, however, hampered by several logistical problems: (1) it is often difficult to bring team members together outside of a fixed meeting time; (2) the number of patients requiring evaluation often requires more time than is available for fixed team meetings; (3) members of the team often turnover; and (4) funding for team members' time or for administrative support is often lacking. A new concept to provide the advantages of a multidisciplinary team while overcoming some of the logistical problems is the use of a clinical pathway (preferably accompanied by electronic order-sets).[143] Clinical pathways may uncover improper diagnostic or therapeutic approaches, or bottlenecks in providing optimal care. Order-sets provide a powerful tool to implement 'bundles' (multiple simultaneous interventions) and to encourage and facilitate optimal and evidence-based care.[144] Although studies to date have been limited to before-and-after designs, teams and order-sets may help to optimize (and minimize) the use of antibiotic agents, reduce costs, and prevent unnecessary amputations.[142]

11. Future research

Increasing antibiotic resistance has stimulated research addressing various types of non-antibiotic treatment for DFIs. Among these, photodynamic inactivation,[145] bactericidal laser therapy,[146] and bacteriophages[147] appear to show promise. Using telemedicine diagnostic support in the home environment may also allow needed foot assessment as well as expert consultative advice. Recently, investigators have developed a photographic foot imaging device for use in home monitoring for the early diagnosis of foot ulcers and pre-ulcerative lesions in diabetic patients.[148] Home monitoring of foot temperatures by infrared thermometry, with modification of activity when the temperature is elevated, has been shown to be reduce foot ulceration in patients with diabetes.[149] Infrared thermal cameras may be useful to detect infections or to predict which patients are at risk of future foot complications,[150] including infections.[151] A study of 38 patients with a diabetic foot complication found that diagnosis based on the combination of photographic and temperature sensing devices was both sensitive and specific, with good intra-observer agreement.[152] Likewise, a quantum dot-based foot mapping system (utilizing a red dot to show the presence of bacteria and a green one to show areas of accumulating inflammation) may help to visualize infection and differentiate it from sterile inflammation.[153] Finally, given the high recurrence rates of neuropathic foot ulcers, helping patients to modify their walking pattern, perhaps with feedback-based approaches, may prove useful.[154] Employing other forms of physical therapy and rehabilitation may also help improve the outcomes of DFI.[155]

12. Conclusions

DFIs are a common, complex, and costly problem that will almost certainly increase in prevalence in the near future. Clinical research over the past three decades has markedly increased our understanding of the pathophysiology, diagnosis, and treatment of both soft tissue and bone infections. The task now is to implement available validated guidelines, to audit processes and outcomes, to educate providers and patients, and to further advance research.

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Bullet points:

- Our understanding of the pathophysiology, diagnosis, and treatment of diabetic foot infections has improved dramatically in the past 30 years.
- The development and validation of guidelines on diabetic foot infections have provided an evidence-based approach to their management.
- We now better know factors that affect the causative pathogens in diabetic foot infections, allowing improved empiric antibiotic therapy.
- Technology has improved our ability to diagnose osteomyelitis of the diabetic foot, and studies have clarified the roles of antibiotic and surgical treatment of this infection.
- Many new technologies are now under evaluation, but the basic principles of properly diagnosing infection, obtaining a specimen for culture, selecting and refining antibiotic therapy, rapidly undertaking the surgical interventions required, ensuring adequate arterial perfusion, and off-loading pressure remain the keys to good outcomes.

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