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Expert Opinion on Pharmacotherapy

ISSN: 1465-6566 (Print) 1744-7666 (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

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To cite this article: Mohamed Abbas, Ilker Uçkay & Benjamin A Lipsky (2015) In diabetic foot infections antibiotics are to treat infection, not to heal wounds, Expert Opinion on Pharmacotherapy, 16:6, 821-832, DOI: 10.1517/14656566.2015.1021780

To link to this article: https://doi.org/10.1517/14656566.2015.1021780

Published online: 03 Mar 2015.

EXPERT OPINION

In diabetic foot infections antibiotics are to treat infection, not to heal wounds

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Introduction: Diabetic foot ulcers, especially when they become infected, are a leading cause of morbidity and may lead to severe consequences, such as amputation. Optimal treatment of these diabetic foot problems usually requires a multidisciplinary approach, typically including wound debridement, pressure off-loading, glycemic control, surgical interventions and occasionally other adjunctive measures.

Areas covered: Antibiotic therapy is required for most clinically infected wounds, but not for uninfected ulcers. Unfortunately, clinicians often prescribe antibiotics when they are not indicated, and even when indicated the regimen is frequently broader spectrum than needed and given for longer than necessary. Many agents are available for intravenous, oral or topical therapy, but no single antibiotic or combination is optimal. Overuse of antibiotics has negative effects for the patient, the health care system and society. Unnecessary antibiotic therapy further promotes the problem of antibiotic resistance.

Expert opinion: The rationale for prescribing topical, oral or parenteral antibiotics for patients with a diabetic foot wound is to treat clinically evident infection. Available published evidence suggests that there is no reason to prescribe antibiotic therapy for an uninfected foot wound as either prophylaxis against infection or in the hope that it will hasten healing of the wound.

Keywords: antibiotic therapy, diabetic foot, foot infection, foot ulcer, topical antimicrobials, wound healing

Expert Opin. Pharmacother. (2015) ***16****(6):821-832*

1. Introduction

Foot ulcers in persons with diabetes are associated with considerable morbidity and are the most important risk factor for developing a diabetic foot infection (DFI) [1]. The development of a diabetic foot ulcer (DFU) is principally related to the presence of peripheral neuropathy and foot deformities [2], often accompanied by peripheral arterial disease and various diabetes-related immunopathies. These diabetes-related complications may impair the host response to infection, making it more difficult to recognize. Optimal treatment of DFU often requires a multidisciplinary team, which may include specialist wound nurse, podiatrist, physical therapist, diabetologist, orthopaedic surgeon, vascular surgeon, and infectious diseases specialists [3]. In Western countries, estimated economic costs related to an episode of DFU published in 2008 generally ranged from $7,000 and $10,000, but may reach up to $65,000 when the wound becomes infected or requires an amputation [4].

Clinically infected wounds, that is, those with evidence of purulent secretions or at least two signs of inflammation, almost always require antibiotic therapy. But, this is only a part of a multimodal approach, which must often include wound

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Article highlights.

- All diabetic foot ulcers are colonized with microorganisms, but only about half are clinically infected at presentation.
- Diagnosis of infection relies on clinical evaluation (evidence of inflammation), not microbiological findings.
- Whereas all wounds need local treatment (e.g., debridement, dressings, pressure-offloading), only infected wounds require antibiotic therapy.
- There is currently no evidence that antibiotic therapy for clinically uninfected wounds reduces the risk of developing an infection or improves wound healing, but such therapy has many potential adverse effects.
- Numerous studies provide evidence for the efficacy of various topical, oral and intravenous antibiotic agents for treating infected foot ulcers, but no one regimen has proven to be superior to others.

This box summarizes key points contained in the article.

debridement (and occasionally more extensive surgical interventions), pressure off-loading, appropriate dressings and various other adjunctive treatments [5]. Unfortunately, the antibiotic therapy prescribed for these diabetic foot wounds is often inappropriate [5]. Many physicians order antimicrobial agents even when they are not certain of the presence of infection. This is usually done for one or more of three reasons: they fear missing an infection; they believe it will reduce the 'bacterial burden' in the wound and thereby promote healing; or, they believe it will prevent the wound from becoming overtly infected. When questioned about this decision, they often respond 'well, it may help, and it can't hurt.'

In fact, inappropriate antibiotic therapy is associated with many serious problems. First, these drugs often cause adverse effects [6], usually related to allergic or direct toxic reactions, or development of antibiotic-associated diarrhea. Second, many antibiotics cause problems by interacting with other drugs; this is a particular problem for patients with diabetes, as they are usually taking many medications. Third, there is a financial cost (which for some new agents can be substantial) associated with antibiotic therapy. But, most importantly, antibiotic-resistant pathogens are becoming a major public health threat and all clinicians must take responsibility for avoiding unnecessary or excessive use of this precious and limited resource. Overuse of antibiotics has been cited by noted authorities [7] as one of the world's most important health concerns, with a real possibility of severely limited availability of effective treatment in the future [8]. It is not by chance that the first (and most of the other) cases of the extreme 'superbug' vancomycin-resistant *Staphylococcus aureus* [9], or many infections caused by virtually untreatable carbapenem-resistant gram-negative rods [10], have been described in diabetic patients with foot problems. Our aim in this paper is to review the available published literature on topical and systemic antibiotic use for infected DFU, with the goal of informing readers about how to appropriately select therapy for these patients.

2. Methods

We conducted a non-systematic search of the English language literature indexed in PubMed from the earliest available papers (1951) through 20 November 2014, using the MeSH terms 'DFI', 'DFU', and with the search term 'antibiotic'. We also searched the EMBASE database, using the following terms: 'topical'/exp OR topical AND ('antibiotics'/exp OR antibiotics) AND ('diabetic'/exp OR diabetic) AND ('foot'/exp OR foot). We reviewed all retrieved titles and abstracts and selected publications that provided original data on all types of studies of any form of antibiotic therapy for diabetic foot wounds. We also reviewed the references of these papers to seek any additional publications that our search missed. As we were only interested in antibiotic drugs, we excluded studies about use of antiseptics [11], honey [12], various wound dressings [11], antimicrobial peptides [13], topical enzymes [11], herbal medications [11], hyperbaric oxygen therapy [14], superoxidized water [15], negative-pressure therapy (vacuum-assisted closure with instillation), antifungal agents [16], antibiotic-impregnated cement, beads [17] or pellets [18], bacteriophages [19] or maggot therapy [20]. We only reviewed studies in humans, and thus excluded all animal or laboratory models. Furthermore, we excluded papers that were primary concerned with surgical approaches [21,22] or photodynamic therapy [23] to treat DFIs.

3. Difficulty in diagnosing infection in diabetic foot wounds

Correctly diagnosing infection of a DFU is crucial, as about half of these wounds are clinically uninfected, and therefore do not need antibiotic therapy [1]. Although identifying microorganisms in aseptically obtained specimens from normally sterile sites is usually diagnostic of infection, all open wounds are colonized with microorganisms, making culture results from these specimens diagnostically non-definitive. Thus, guidelines for wounds recommend using clinical findings to diagnose infection. Diabetic foot wounds are problematic, however, because the presence of peripheral neuropathy or foot ischemia can either diminish or mimic inflammatory findings, reducing their usefulness. Furthermore, other inflammatory conditions, for example, acute Charcot foot syndrome or gout attack, can be difficult to distinguish from infection.

Patients with a DFI typically have a history of a recent break in the protective skin envelope, followed over time (sometimes hours, more often days or even weeks) by spreading inflammation [24]. These wounds may be caused by mechanical, chemical or thermal trauma, but are most often due to pressure. DFIs are generally defined by a constellation of clinical symptoms [25] compatible with a local infectious

syndrome: erythema (rubor), warmth (calor), swelling (tumor), pain or tenderness (dolor), or purulent secretions. Systemic findings (e.g., fever, chills, leukocytosis, hypotension, tachycardia, tachypnea) are infrequent and indicative of a severe infection. Based on available evidence, the 2012 guidelines on DFIs produced by both the Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot advocate defining infection as the presence of purulence or at least two of the above-mentioned classic findings of inflammation [5].

Infection of soft tissues often spreads contiguously to underlying bone. This diabetic foot wound-related osteomyelitis may be suspected on physical examination [26] by the presence of a 'sausage toe,' that is, a red, swollen, warm digit. The only virtually pathognomonic clinical sign of osteomyelitis, however, is the presence of fragments of bone extruding from a sinus tract, often seen on the dressing, or found during debridement. In contrast to long bones, osteomyelitis of the small bones of the foot often lacks a sequestrum or sinus tract [27] that can be easily distinguished from an overlying ulcer. The probe-to-bone test, striking bone when probing a wound, can be helpful in diagnosing diabetic foot osteomyelitis, but only if it is correctly performed (using a blunt metal probe) and interpreted (with consideration of the pre-test probability of osteomyelitis). Bone changes in osteomyelitis take at least 2 to 3 weeks before being visible on plain x-rays. Substantial elevations of serum inflammatory markers, especially the erythrocyte sedimentation rate, suggest bone infection, but are often absent in DFI, especially in chronic cases.

4. When to use antibiotics?

DFU and DFI are epiphenomena of the syndrome of the diabetic foot, and thus complications of long-standing hyperglycemia, peripheral neuropathy and arterial insufficiency. Clinically uninfected DFU usually heal without antibiotic therapy if properly treated. This means appropriate wound care, generally including cleansing, debridement, appropriate dressings to maintain a moist wound bed, pressure off-loading, and improved glycemic control [2]. These measures, in addition to antibiotic therapy, are also key to healing infected wounds [28]. Before antibiotic therapy was available, DFIs frequently resulted in major (most often above-the-knee) limb amputations and occasional mortality. In this pre-antibiotic era surgical interventions were the mainstay of treatment. Many moderate, and almost all severe, DFIs continue to require surgical interventions, ranging from deep debridement or incision and drainage to resection of bone and revascularization. Some studies suggest that early surgical interventions for selected DFIs may limit the duration of antibiotic therapy and result in better outcomes. A more comprehensive discussion of indications for surgery and the timing of the intervention is beyond the scope of this paper and has been dealt with by Dalla Paola *et al.* [29] and Chaytor *et al.* [30].

Diabetic foot osteomyelitis is particularly difficult to treat, and its presence markedly increases the risk of lower extremity amputation. Until recently, most of these patients underwent surgical resection of the infected and necrotic bone. In the past decade, however, retrospective reviews have demonstrated that about two-thirds of selected patients with diabetic foot osteomyelitis can achieve a remission of infections with antibiotic therapy alone [31]. Indeed, a recent small randomized clinical trial in patients with diabetic foot osteomyelitis found that treating with antibiotic therapy (given for 90 days) without surgical intervention gave similar clinical outcomes to treatment with conservative surgery (removal only of the infected bone) with just a short course of antibiotic therapy [21]. A recently published randomized controlled trial compared a 6-week against a 12-week duration of antibiotic therapy, without concomitant surgery, for diabetic foot osteomyelitis [32]. The results of this study showed no difference in rates of remission or relapse between the two groups, suggesting that treatment for longer than 6 weeks may not be necessary. These and other studies have brought some clarity to the question of which patients may be offered exclusively medical (antibiotic) versus primarily surgical treatment [33].

Because of the difficulty in healing some DFUs, many physicians and surgeons prescribe antibacterial chemotherapy even for clinically uninfected wounds. This is usually done in hopes of accelerating healing (by lowering the 'bioburden' of bacteria in the wound) and preventing clinically overt infection. Certainly antimicrobials inhibit or kill susceptible bacteria, and some may even exert anti-toxigenic or anti-inflammatory effects in DFI [34]. However, there are no convincing published data to support they offer any clinical benefits. One double-blind, placebo-controlled trial in which 39 patients with an 'uncomplicated' neuropathic DFU were treated with either antibiotic therapy (oral amoxicillin/clavulanate) or placebo found no difference in the wound healing rate (relative risk 0.63, 95% CI: 0.29, 1.40) [35]. Similarly, a study of patients with neuropathic foot ulcers found no significant difference in ulcer healing for 25 patients treated with parenteral antibiotic therapy (ceftriaxone) compared to 25 historical controls not treated with antibiotics (relative risk 1.45, 95% CI 0.86, 2.47) [36].

Conversely, antibiotic therapy is certainly associated with several potentially important adverse effects. These agents are relatively frequent causes of direct toxic effects, such as rashes, renal dysfunction, *Clostridium difficile* disease and even anaphylaxis. Furthermore, they can interact with other medications to cause drug-related problems. Given how many medications most persons with diabetes take, this is a substantial concern. Antibiotics can also alter a person's resident skin flora and impair some aspects of the innate immune system; these effects have been shown in experimental models to ultimately lead to delayed wound repair [37]. The relationship between antibiotic consumption and resistance is well

established [38-41]; therefore, clinicians should avoid unnecessary antibiotic use in order to minimize the prevalence of resistant bacteria. Finally, antibiotic therapy incurs financial costs, which can be quite high for certain new agents. Hence, clinicians must balance the risk to benefit equation each time they consider an antibiotic prescription for a DFU. Although none would argue against treating moderate and severe DFIs with antibiotic therapy, there is some doubt as to whether or not it is needed for all mildly infected DFUs. Currently, there are on-going clinical trials to address this issue by comparing treatment with either an active topical antimicrobial or a placebo (in addition to standard wound care) for such patients.

4.1 Bacterial burden in diabetic foot ulcers

In some cases DFU do not heal despite clinicians providing patient education, optimized glycemic control, local wound care, pressure off-loading and treatment of any vasculopathy. These ulcers may give off a foul odor, be covered by fibrin [8], exude serous fluid, show undermining of the wound rim, or have discolored or friable granulation tissue [42]. Some authorities believe these are 'secondary' signs of infection, particularly in patients with peripheral neuropathy or vasculopathy, or with high levels (> 10^5 colony forming units per gram of tissue) of bacterial colonization, often called 'critical colonization' or high 'bacterial burden' [4,8]. Whether such a phenomenon exists, and if so exactly how it should be defined, are controversial subjects. Two small studies of patients with a DFU found a negative correlation between bacterial load and the likelihood of wound healing during a specified period of observation [43,44]. Although these studies showed a correlation, they do not prove causation. One study that used electron microscopy found a higher number of microbial aggregates in non-healing wounds compared with acute wounds [45]. But, it is unclear if non-healing wounds have more time to be colonized with bacteria or if the presence of high levels of bacteria causes the chronicity.

A recent Cochrane review found no evidence favoring the use of antibiotic treatment for heavily contaminated, but clinically uninfected, venous leg ulcers [46]. Diabetic foot experts [47], including the authors of the most recent guidelines on DFI [5,48], the European Wound Management Associations' policy [8] and the Scottish consensus statement [49], do not recommend treating uninfected DFU with antibiotic therapy, as the risk of harm almost certainly outweighs any possible benefit. Clearly, we need more and larger studies of this issue to determine if lowering microbial load improves ulcer healing.

Nevertheless, many clinicians feel compelled to prescribe antibiotics for chronic, especially non-healing wounds. Reasons for this 'non-pharmacological' prescribing of antibiotics include: their lack of confidence in the face of uncertainty about the presence of infection; pressure from patients or family; work pressure and fatigue; and various organizational factors [50]. But, clinicians can be successfully taught to reduce unnecessary prescribing of antibiotics. A recent large registry study in Sweden [51] has shown that providing web-based information on appropriate ulcer care was associated with a highly significant reduction of antibiotic prescribing for these wounds, from 71 to 29%. Other methods that have been shown to improve physicians' antibiotic prescribing include deploying 'academic detailing,' and interdisciplinary quality improvement teams [52,53].

4.2 Biofilm

A key factor contributing both to delaying wound healing and in eradicating microorganisms is the presence of bacteria in a biofilm state. In this matrix, composed of a multitude of proteins, sugars and other materials, bacteria live in colonies protected from mechanical, cellular and chemical attack by host defences, leukocytes or antibiotics [54]. Microbial biofilms appear to play a role in DFI involving both soft tissue and bone and their presence is associated with the failure of these wounds to heal [55]. In a study from India, 68% of DFI were associated with biofilm production [56]. The presence of biofilm in this study was significantly associated with male sex, duration of the DFU, presence of a necrotic ulcer, and especially polymicrobial infection [56]. In contrast to the available epidemiological data on biofilms in orthopaedic implant-associated infection [57], we still lack a clear understanding of the proper intervention for biofilms in non-healing DFU or DFI in the absence of a foreign material [8]. So far, only experimental studies of chemical therapeutic agents aimed at biofilm in the diabetic foot are available [58,59].

4.3 Prophylactic antibiotic treatment

As with most surgical interventions, correct perioperative antibiotic prophylaxis should be beneficial for orthopedic (implant-related) operative procedures on the diabetic foot [60]. We were unable, however, to find any studies investigating the role of surgical antibiotic prophylaxis specifically targeted for diabetic foot procedures. Some pathogens that are frequently isolated from DFU, such as *Pseudomonas aeruginosa* or MRSA, are considered difficult to eradicate in bone-related infections, especially when there is osteosynthetic material involved [61,62]. The situation seems to be different in the diabetic foot, where several studies have shown that most patients with these isolates improve despite therapy with antibiotics ineffective against the organisms [5]. Moreover, healthcare-associated MRSA isolates are not more virulent than methicillin-susceptible *S. aureus* isolates in the diabetic foot [63]. Indeed, production of staphylococcal toxins and other virulence factors is more common in the presence of an implant, compared to soft tissue infections and implant-free, osteomyelitis, including in the diabetic foot [64].

5. Antibiotic treatment in overt diabetic foot infection

When there is overt clinical evidence of infection in a diabetic foot wound, antimicrobial therapy is virtually always

appropriate [25]. Clinicians can choose from a wide variety of antimicrobial agents, which may be administered parenterally (intramuscularly, but more often intravenously), orally or topically. Despite many studies of antimicrobial therapy for DFIs, no one agent or combination has emerged as optimal [25,65-67]. The appropriate duration of antibiotic therapy ranges from a week or two for most mild soft tissue infections, to 4 to 6 weeks in cases of osteomyelitis that have not had resection of infected bone [25]. As antibiotics are only used to treat infections, they should be discontinued when clinical signs of infection have resolved, rather than waiting until the ulcer heals (which may take months).

Clinicians must choose an empiric regimen by considering the most likely pathogens [68], the local epidemiology (of causative organisms and their susceptibility), the availability of specific antibiotic drugs, any patient co-morbidities and recent culture results [63], the severity of infection [5], the duration of the ulcer as well as its clinical presentation [69]. When culture and sensitivity results are available, definitive therapy should be based both on these results and the patient's clinical response to the empiric therapy. Patients with a DFI who are referred to a diabetic foot clinic have usually been treated with antibiotics before microbiological samples are obtained; this diminishes the accuracy of microbiological results. The IDSA guidelines [5] recommend obtaining deep tissue samples for culture, either by biopsy or curettage, as superficial swabs provide less accurate results. We eagerly await reports of the results of a large, multicentre prospective study comparing the concordance of culture results between superficial swabs and deep tissue specimens in DFI [70] that has been completed. Optimally, clinicians should attempt to constrain the spectrum of treatment, using the safest and least expensive drugs available, and treat for the shortest duration necessary.

5.1 Topical antibiotics

Superficial, open wounds without extensive cellulitis can potentially be treated with topical antimicrobials. The advantages of topical therapy include the ability to deliver a high local concentration with small doses of the agent, even in patients with limb ischemia, to avoid the first-pass effect in the gastrointestinal tract, as well as reducing risks of systemic side effects. Relatively few studies of topical therapy for DFI have been published [13,71-73], with a PubMed search revealing only 31 papers, which used a variety of antibiotics, such as mupirocin, bacitracin, neomycin, chloramphenicol, polymyxin B, and gentamicin. Interestingly, for DFI we did not identify any publications reporting on the use of topical fusidic acid, an antibiotic often misused in cases of non-DFI superficial skin infections and furunculosis in many parts of the world [74]. The results of published studies of topical therapy comparing an active agent to placebo, active agents to one another, or as adjuncts to systemic antibiotic therapy, have showed mixed results [75]. As topical agents are typically applied in mild DFI (or uninfected DFU), it is difficult to distinguish their clinical benefits from those of local wound care alone. The eradication or reduction of microorganisms in the wound alone is not a sufficient endpoint for their efficacy [8], any more than their presence is a definition of clinical infection. Lastly, no clinical data support the use of topical antibiotic treatment for prevention of wound infection recurrences [8]. However, the distinction between true recurrences and new episodes is difficult, especially in view of the polymicrobial and complex nature of DFIs.

Gentamicin, either in an ointment or embedded in a sponge, is a promising agent [4] as it is active against many of the gram-positive and gram-negative pathogens found in DFI. The topical formulation achieves very high local concentrations, but is not systemically absorbed so does not pose the risks associated with intravenous therapy [4]. A pilot study of treatment in 56 DFI patients found that adding a topical gentamicin-collagen sponge to systemic antibiotic therapy, compared to systemic antibiotics alone (for up to 28 days), produced a higher cure rate (100 vs 70%) 2 weeks after the end of therapy [71]. The addition of the gentamicin-collagen sponge also significantly improved eradication of baseline pathogens and reduced the time to pathogen eradication [71]. Another randomized trial on stump wounds examined the value of adding a gentamicin-collagen sponge to systemic antibiotic therapy after a minor foot amputation in 50 patients with a DFI [72]. Those who received the gentamicin-collagen sponge had a significantly shorter (by almost 2 weeks) median wound healing time compared to those who did not [72]. The largest study of topical antimicrobial therapy in patients with a DFI (with 835 evaluable patients) compared treatment with a topical investigational antimicrobial peptide (pexiganan) against an oral fluoroquinolone (ofloxacin) [13,73]. The rates of clinical cure, pathogen eradication and wound healing were similar in the two treatment arms. Some international guidelines suggest that topical agents may occasionally be helpful but do not strongly support them [5,76], whereas other national consensus do not even mention them [49].

5.2 Oral antibiotics

For severe infections, or in patients unable to take oral medications, parenteral (usually intravenous) therapy is generally preferred, at least initially. In our review of the literature we found no published study supporting the superiority of a parenteral over an oral antibiotic regimen, even in patients with limited arterial blood flow in the lower extremities. Nevertheless, despite the lack of data, almost all patients who present with severe DFI should be treated with parenteral antibiotics, at least initially. In uncomplicated DFI, several studies support the efficacy of regimens with just oral antibiotic therapy [68]. Several prospective trials have shown that approximately three-quarters of DFI patients can be cured by oral antibiotics alone [21,77]. These data are confirmed by many prospective and retrospective observational studies, for both soft tissue and bone infections [78-84]. One prospective case series of oral antibiotics alone (ofloxacin and rifampicin) for the treatment of diabetic foot osteomyelitis found a clinical

cure rate of 88% [81]. A Cochrane review and meta-analysis found no difference in outcomes between oral and intravenous antibiotics for treating various types of chronic osteomyelitis [85]. The most frequently studied oral antibiotic agents for treating DFI are amoxicillin-clavulanate and moxifloxacin.

5.3 Parenteral antibiotics

Many randomized trials provide evidence of the effectiveness of various parenteral antibiotics for DFI, often with switch to oral therapy after the patient is improving [86-98]. Unfortunately, in these studies the enrolled populations, study designs and outcome definitions are too heterogeneous allow direct comparisons. Parenteral treatment durations ranged from 6 to 24 days. Some studies excluded osteomyelitis and wounds with higher severity scores, potentially leading to higher success rates [87,88,90,92,98]. Antibiotic regimens in some studies focused on *Staphylococcus aureus* (including MRSA) [89,91], but most included broad-spectrum antibiotics that cover both gram-positive and gram-negative bacteria [86-88,90,92,93,95-98].

In the light of the increased rate of infections caused by MRSA, several studies examined agents active against this pathogen. In one study, linezolid (active against only gram-positive organisms, including MRSA) was found to be at least as effective in curing infections and eradicating pathogens as an aminopenicillin/beta-lactamase inhibitor (relatively broad-spectrum but lacking MRSA activity) [89]. Although other specified antibiotics active against either gram-negative organisms (for the patients on linezolid) or MRSA (for the patients on the comparator) could have been added, they rarely were. Another study retrospectively analyzed data on a subset of patients with DFI from a prospective randomized controlled trial of skin and soft-tissue infections that compared daptomycin, another intravenous agent active against MRSA, to vancomycin (for patients with MRSA infection) or a semi-synthetic penicillin (for patients with a methicillin-sensitive infection) [91]. The clinical and microbiological efficacy was similar in all study arms. In one study of DFI, patients were randomized to ertapenem (which is not active against *Pseudomonas aeruginosa*) or to piperacillin/tazobactam (which does cover *P. aeruginosa*) [90]. The results showed that patients receiving ertapenem from whom *P. aeruginosa* was isolated had similar cure rates to the piperacillin/tazobactam-treated patients. In another study, moxifloxacin had comparable outcomes to piperacillin/tazobactam or amoxicillin/clavulanate [77]. The most extensively investigated drugs, however, have been various beta-lactams compared against one other [86,88,90,92,93,96] or with a fluoroquinolone [87,94,95,97]. Among these, six studies allowed an oral switch after the patients' condition had improved [87,89,90,94,95,97]. Overall, for moderate-to-severe DFI, studies with intravenous antibiotics had clinical remission rates from 50 to 85% (**Table 1**).

6. Conclusions

DFU and DFI are leading causes of morbidity, including lower extremity amputations. These wounds are optimally treated by a multidisciplinary team, providing debridement, off-loading, and correction of ischemia, if needed. Antibiotic therapy is required for virtually all infected diabetic foot wounds, but there is no compelling evidence that treating clinically uninfected wounds either accelerates healing or prevents the development of active infection. Considering the financial costs, potential adverse clinical and societal consequences of antibiotic therapy and the risk-benefit ratio of treating clinically uninfected wounds with antibiotic therapy, we think this practice is unacceptable. Infected wounds can be treated with topical, oral or parenteral antibiotic agents, depending on the severity of the infection and other factors. Many studies have demonstrated the effectiveness of various agents administered by each of these routes, but no agent or combination has emerged as optimal. To reduce the likelihood of encouraging antibiotic resistance, therapy should be focused on the cultured pathogens and be given for the shortest duration necessary. They can be discontinued when clinical signs and symptoms of infection have resolved, rather than continuing them until the wound is healed.

7. Expert opinion

Diabetic foot ulceration and infection are epiphenomena and the ultimate consequences of an underlying multifactorial disease characterized by the metabolic consequences of chronic hyperglycemia, ill-defined and varied types of immune suppression, peripheral neuropathy and arterial insufficiency. Unlike many infections, there are no microbiological or laboratory tests by which one can diagnose DFI, and cure of infection requires a multimodal approach, not just antimicrobial therapy. Most DFI begin in a wound, usually an ulcer, but only about half of DFUs are clinically infected on presentation. Because all wounds are colonized, we define infection by the presence of clinical findings of inflammation. However, the perturbations related to diabetic complications may diminish the host response, leaving clinicians uncertain which wounds are infected.

Antibacterial agents are certainly needed for treatment of all moderate and severe DFI, and likely for the great majority of mild infections as well. Because of the difficulty in diagnosing infection in diabetic foot wounds and the potentially catastrophic outcomes of failing to properly treat them, many clinicians feel compelled to treat virtually all of them with antimicrobial therapy. This is often done with one of several rationalizations. Many say, 'the wound may have a high bioburden (or critical colonization) and this impairs wound healing.' Or, 'the wound may be uninfected now, but unless treated with antimicrobials it will likely become infected.' In some cases it is the patient or a family member who insist

Table 1. Summary of selected studies on antibiotic treatment for diabetic foot infections and diabetic foot osteomyelitis.

Author (year)	Study design	Infection type (number enrolled)	Osteomyelitis excluded?	Antibiotic agent (no. of patients)	Intravenous treatment (%)	Duration of therapy	Clinical remission (%)	Surgery, type (%)	Follow-up duration
Randomized-controlled trials of topical therapy									
Lipsky *et al.* (2008) [13]	Randomized	DFI (835)	Yes	Ofloxacin (417) Pexiganan	0%	22 – 27 days	95%	Amputation 2.4%	14 days after EOT
Lipsky *et al.* (2012) [71]	Randomized	DFI (56)	Yes	Gentamicin-collagen sponge No sponge	0%	20 days	100%	N.A.	14 days after EOT
Varga *et al.* (2014) [72]	Randomized	DFO (50)	N.A.	Gentamicin sponge (25) No sponge (25)	0%	N.A.	???	Amputation 100%	1 month
Randomized-controlled trials of oral therapy only									
Peterson *et al.* (1989) [100]	Randomized	DFI (48)	No	Ciprofloxacin low-dose (23) Ciprofloxacin high-dose (22)	0%	3 months	52% 68%	Amputation 19%	1 year
Lipsky *et al.* (1990) [77]	Randomized	DFI (60)	No	Cephalexin (29) Clindamycin (27)	0%	2 weeks	72% 78%	34% minor surgery	15 ± 9 months
Chantelau *et al.* (1996) [35]	Randomized	DFU (44)	Yes	Amoxicillin-clavulanate (19) Placebo (20)	0%	20 days	32% 50%	N.A.	At EOT
Lázaro-Martinez *et al.* (2014) [21]	Randomized	DFO (52)	N.A.	Oral antibiotics, prolonged (25) Surgery, antibiotics, short (27)	0%	90 days 10 days	75% 86%	0% 100% conservative	12 weeks after EOT
Randomized-controlled trials with at least some intravenous therapy									
Grayson *et al.* 1994 [86]	Randomized	DFI (97)	No	Ampicillin-sulbactam (48) Imipenem (48)	100%	12 – 13 days	81% 85%	Amputation 64%	1 year
Lipsky *et al.* (1997) [87]	Randomized	DFI (108)	Yes	Ofloxacin (47) Ampicillin-sulbactam (41)	100%	12 – 13 days	85% 83%	Surgery 71%	3 – 5 days after EOT
Clay *et al.* (2004) [88]	Randomized	DFI (70)	Yes	Metronidazole + ceftriaxone (36) Ticarcillin-clavulanate (34)	100%	6 ± 4 days	72% 76%	N.A.	20 – 28 days after enrolment
Lipsky *et al.* 2004 [89]	Randomized	DFI (371)	No	Linezolid (203) Ampicillin-sulbactam (108)	All patients had I.V. with oral switch	17 days (mean)	81% 71%	N.A.	15 – 21 days after EOT
Lipsky *et al.* 2005) [90]	Randomized	DFI (514)	Yes	Ertapenem (206) Piperacillin-tazobactam (196)	67% of patients switched to oral therapy	11 days	94% 92%	N.A.	10 days after EOT
Lipsky *et al.* (2005) [91]	Randomized	DFI (133)	Yes	Daptomycin (47) Vancomycin (29) or semi-synthetic penicillin (27)	100%	7 – 14 days	66% 70%	N.A.	20 – 28 days after enrollment
Harkless *et al.* (2005) [92]	Randomized	DFI (300)	Yes	Piperacillin-tazobactam (96) Ampicillin-sulbactam (89)	100%	8 days	81% 83%	Amputation 10%	14 – 21 days after EOT
Embil *et al.* (2006) [93]	Randomized	DFI (83)	N.A.	Meropenem (44) Imipenem (39)	100%	6 days	52% 86%	Amputation 3% Surgery 63%	7 – 14 days after EOT

DFI: Diabetic foot infection; DFO: Diabetic foot osteomyelitis; EOT: End of therapy; I.V.: Intravenous; N.A.: Not applicable or not available; TOC: Test-of-cure (visit).

Table 1. Summary of selected studies on antibiotic treatment for diabetic foot infections and diabetic foot osteomyelitis (continued).

Author (year)	Study design	Infection type (number enrolled)	Osteomyelitis excluded?	Antibiotic agent (no. of patients)	Intravenous treatment (%)	Duration of therapy	Clinical remission (%)	Surgery, type (%)	Follow-up duration
Lipsky *et al.* (2007) [94]	Randomized	DFI (127)	Yes	Moxifloxacin (63) Piperacillin-tazobactam/amoxicillin-clavulanate (64)	59% oral 67% oral	6 – 8 days	67% 61%	Amputation 12 – 16%	10 – 42 days after EOT
Vick-Fragoso *et al.* (2009) [95]	Randomized	DFI (134)	No	Moxifloxacin (63) Amoxicillin-clavulanate (71)	All patients had I.V. with oral switch	15 days	51% 67%	N.A.	14 – 28 days after EOT
Saltoğlu *et al.* (2010) [96]	Randomized	DFI (64)	No	Piperacillin-tazobactam (30) Imipenem (32)	100%	24 days	47% 28%	Amputation 60% Amputation 69%	2 months
Schaper *et al.* (2013) [97]	Randomized	DFI (233)	No	Moxifloxacin (63) Piperacillin-tazobactam (64)	All patients had I.V. with oral switch	8 days	76% 78%	Minor surgery 13% Amputation 12%	14 – 28 days after EOT
Lauf *et al.* (2014) [98]	Randomized	DFI (955)	Yes	Tigecycline (476) Ertapenem (466)	100%	11 – 12 days (median)	71% 78%	N.A.	12 – 92 days
	Randomized (substudy)	DFO (118)	N.A.	Tigecycline (53) Ertapenem (33)	100%	39 days	36% 64%	N.A.	26 weeks
Observational (prospective or retrospective) studies									
Diamantopoulous *et al.* (1998) [78]	Prospective observational	DFI (84)	No	Ciprofloxacin + clindamycin (84)	All patients had I.V. with oral switch	N.A.	77%	Amputation 14%	16 months (mean)
Pittet *et al.* (1999) [79]	Retrospective cohort	DFI (120)	No	Antibiotics (91)	N.A.	I.V. 24 days oral 6 weeks	63%	N.A.	24 months
Senneville *et al.* (2001) [81]	Prospective case series	DFO (31)	N.A.	Ofloxacin + rifampicin (17)	0%	Median 6 months	88%	Surgery 12%	22 months
Embil *et al.* (2006) [101]	Retrospective case series	DFO (94)	N.A.	Various antibiotics (93)	31%	13 days	87%	Amputation 10 % Surgery 28%	50 weeks
Senneville *et al.* (2008) [80]	Retrospective case series	DFO (59)	N.A.	Various antibiotics (50)	32%	12 ± 4 weeks	64%	Amputation 6%	12 months
Game *et al.* (2008) [82]	Retrospective case series	DFO (137)	N.A.	Amoxicillin-clavulanate (57) Fluoroquinolone + clindamycin (52)	18%	I.V. 16 days oral 61 days	58%	Amputation 7%	12 months
Acharya *et al.* (2013) [83]	Retrospective case series	DFO (130)	N.A.	Various antibiotics (130)	8%	N.a.	67%	Amputation 14%	12 months
Bogner *et al.* (2013) [84]	Prospective observational	DFI (1103)	N.A.	Moxifloxacin (1103)	14%	I.V. 9 days oral 13 days	83%	N.A.	N.A.
Lipsky *et al.* (2014) [102]	Retrospective observational	DFI (201)	Yes	Ceftaroline (201)	100%	Mean 6.1 days (1 – 30)	81%	47% (various types)	N.A.

DFI: Diabetic foot infection; DFO: Diabetic foot osteomyelitis; EOT: End of therapy; I.V.: Intravenous; N.A.: Not applicable or not available; TOC: Test-of-cure (visit).

on antibiotic therapy for an uninfected foot wound. Probably no physician can claim never to have 'given in' when faced with desperate situations where the success of treatment is not immediately visible and prescribing an antibiotic is easy compared to other measures, such as providing patient education. Hence, among all therapeutic measures, antibiotics are ironically among the only ones prone to overuse (despite the fact that infection is an epiphenomenon), whereas the other recommendations are generally underused (followed inconsistently, partially or temporarily). Underlying this unnecessary treatment is often the belief that 'even if antibiotics don't help, they won't hurt.' This is clearly not the case, as we now know that antibiotic treatment is associated with frequent adverse effects for the patient and with the growing problem of antibiotic resistance. Thus, we have to persuade clinicians, patients and family members that whereas uninfected diabetic foot wounds certainly require various kinds of treatment and careful follow-up, antibiotic therapy will more likely do harm than good.

When antibiotic therapy is needed for clinically infected diabetic foot wounds, it must be based on scientific evidence. Due to the nature of diabetic foot problems, we currently lack sophisticated randomized trials to inform decisions about optimal agents, routes of administration, dosing regimens, duration of therapy, or ways of assessing when infection has resolved. Proper studies are difficult to perform because of the varied case-mix of the presenting study population, for example, type of diabetes, presence of foot ischemia, duration of foot wound, or recent antimicrobial therapy. Furthermore, it is unclear how to best define key outcomes of treatment, for example, when to assess for cure, the importance of microbial eradication, the effect on wound healing. The currently available studies on patients with DFI suggest that with proper antimicrobial therapy, wound care and surgical procedures, the great majority can be cured. Unfortunately, the highest likelihood predictor of a DFI is a history of a previous DFI, so these patients remain at high risk. Thus, they need clear and repeated education on how to prevent foot complications and how to respond if they develop one. We hope that part of that education will be teaching patients and their families that antibiotics are for treating infection, not for healing wounds.

Declaration of interest

B Lipsky has acted as consultant for KCI/Acelity, Innocoll, Dipexium, Merk and Pfizer. I Uçkay has received research funding from Innocoll. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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