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SUPPLEMENT ARTICLE

Diabetic foot infections: Current treatment and delaying the 'post-antibiotic era'

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Abstract

Background Treatment for diabetic foot infections requires properly diagnosing infection, obtaining an appropriate specimen for culture, assessing for any needed surgical procedures and selecting an empiric antibiotic regimen. Therapy will often need to be modified based on results of culture and sensitivity testing. Because of excessive and inappropriate use of antibiotics for treating diabetic foot infections, resistance to the usually employed bacteria has been increasing to alarming levels.

Review This article reviews recommendations from evidence-based guidelines, informed by results of systematic reviews, on treating diabetic foot infections. Data from the pre-antibiotic era reported rates of mortality of about 9% and of high-level leg amputations of about 70%. Outcomes have greatly improved with appropriate antibiotic therapy. While there are now many oral and parenteral antibiotic agents that have demonstrated efficacy in treating diabetic foot infections, the rate of infection with multidrug-resistant pathogens is growing. This problem requires a multi-focal approach, including providing education to both clinicians and patients, developing robust antimicrobial stewardship programmes and using new diagnostic and therapeutic technologies. Recently, new methods have been developed to find novel antibiotic agents and to resurrect old treatments, like bacteriophages, for treating these difficult infections.

Conclusion Medical and political leaders have recognized the serious global threat posed by the growing problem of antibiotic resistance. By a multipronged approach that includes exerting administrative pressure on clinicians to do the right thing, investing in new technologies and encouraging the profitable development of new antimicrobials, we may be able to stave off the coming 'post-antibiotic era'. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords infection; diabetic foot infection; antibiotic therapy; antibiotic resistance; post-antibiotic era

'A post-antibiotic era means…an end to modern medicine as we know it.'
Dr. Margaret Chan, OBE, MD, DSc
Director-General, World Health Organization
Copenhagen, Denmark, 14 March 2012

Introduction

Foot complications are a major, and increasingly frequent, complication of diabetes mellitus. Estimates are that among the ~9% of all people in most

countries who have diabetes, about 25% will develop a foot complication [1]. The most recently available data from the United States Centers for Diseases Control and Prevention have shown that while the previous steady rise in number of hospital discharges for diabetic lower extremity complications has levelled off to below 900 000/year, the major cause of these hospitalizations is now 'ulcer/inflammation/infection' [2]. The most common foot problem is an ulceration of the skin, usually related to peripheral neuropathy (particularly sensory, but also motor and autonomic), often accompanied by peripheral arterial disease. Other factors, such as metabolic perturbations, immunopathies and impaired wound healing, often contribute to these problems. Most typically, after an insensate foot is exposed to trauma (pressure, thermal, chemical, blunt or sharp blows), there is a disruption of the protective skin envelope, allowing colonization of the subcutaneous tissues. In about half of these cases, the wound will become clinically infected, requiring antimicrobial therapy, and often some form of surgical procedure.

Approach to treatment of diabetic foot infection

The goal of treatment for a diabetic foot infection (DFI) is to limit the destruction caused by invading pathogens, as well as the host inflammatory response they induce. We classify DFI by their clinical severity, ranging from mild (~35% of cases, depending on site of presentation), through moderate (~30%–60%), to severe (~5%–25%) [3]. This classification determines several key issues: (1) how urgent it is to initiate treatment, (2) in what setting to provide the treatment, (3) if it is necessary to undertake immediate surgical treatment, (4) how broad-spectrum empiric antibiotic therapy should be, and (5) the appropriate route of administration of antimicrobial therapy. A patient with a DFI should have a careful physical examination, specifically including the foot (especially for evidence of neuropathy and peripheral vascular disease) and the wound (to document any signs of infection and to probe for evidence of bone involvement). Those with a moderate or severe infection should have blood tests for basic chemistries and a complete blood count; an erythrocyte sedimentation rate and perhaps C-reactive protein may help in assessing and following the infection. After cleansing the wound with saline, the clinician should obtain a specimen (of tissue, if at all possible) to send for aerobic and anaerobic culture. Plain x-rays can demonstrate foreign material, tissue gas or bony involvement.

After assessing the patient, foot and wound, the clinician must quickly decide if surgical consultation is needed to determine if any urgent operative procedure is required. Almost all wounds should be cleansed and debrided, but many may require incision and drainage, deep tissue or bone resection, or limb revascularization. The presence of a deep abscess, rapidly spreading infection, compartment syndrome or possible necrotizing fasciitis should prompt immediate surgery.

While awaiting results of any further diagnostic testing or consultations, the clinician must select an empiric antibiotic regimen. The choice should be largely based on the severity of the infection and consideration of the likeliest pathogens in the individual patient. This requires reviewing the patient's current geographic location, risks of exposure to unusual or highly resistant organisms, any co-morbid medical problems and any recent antimicrobial treatment. Of course, the antibiotic selection must take into account which agents have demonstrated efficacy in treating DFIs, what agents are available in the specific treatment setting, and any relevant patient allergies or co-morbidities. Although mild infections can usually be treated with an oral (or occasionally a topical) antibiotic, most moderate and all severe infections should initially be treated with parenteral therapy, with a switch to oral agents when the patient is clinically stable. For patients without a risk factor for unusual or resistant pathogens, early generation beta-lactam antibiotics (semi-synthetic penicillins or cephalosporins) are sufficient in most Western countries, while coverage for aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*) is advisable in many Asian and African countries [4]. When the wound has a putrid odour or is accompanied by gangrene or ischemia, it is prudent to add an anti-anaerobic agent [5]. In a patient likely to have an unusual or resistant pathogen, it is safest to treat with a broader-spectrum regimen (e.g. an anti-pseudomonal beta-lactam, beta-lactamase inhibitor, a group 2 carbapenem or an advanced generation cephalosporin) to start, while obtaining proper specimens for culture and sensitivity. When these results are available, the clinician should review them, and the patient's clinical response to the empiric regimen, and attempt to more accurately target (and preferably constrain) the antibiotic regimen. Infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are a problem in some centers; new diagnostic techniques, such as using real-time polymerase chain reaction on fluids and tissue, can rapidly detect these organisms and potentially reduce empirical use of anti-MRSA antibiotics. [6]

Clinicians should consider selecting less expensive, but equally effective, agents, when possible. Furthermore, they should bear in mind that some agents, such as fluoroquinolones, may be more likely to facilitate the emergence of bacterial resistance. It is also important to carefully monitor the effectiveness of treatment of the

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DFI. If the local (and any systemic) signs and symptoms are not responding within 2–3 days, reconsider the need for surgery, for more advanced imaging studies or for further vascular evaluation. In addition, reassess the antibiotic regimen, specifically considering if there are organisms that were not covered by the current agents, or if the initial specimen for culture was suboptimal. Repeat cultures, especially of deep tissues, may reveal pathogens that were missed previously. Some preliminary data suggest that patients colonized (in the anterior nares or rectum) with multidrug-resistant pathogens (e.g. MRSA [7] or extended-spectrum beta-lactamase producing gram-negative bacilli [8]) are at higher risk for infection with these organisms, even if they have not been isolated from a wound infection. In this case, changing antibiotics to one that covers these organisms may be justifiable, but blindly switching to a 'more powerful' agent is rarely helpful. No data support bactericidal antibiotics being more effective than bacteriostatic agents for treating wound infections in a non-immunocompromised host [9]. I have provided a simplified approach to antibiotic therapy of diabetic foot infections in Figure 1.

Once the patient's DFI is responding to treatment, the clinician must consider the duration of antibiotic therapy needed. Several factors suggest clinicians should keep the duration of therapy as short as possible: antibiotic treatment is often associated with adverse effects; antibiotics can interact with other medications the patient is taking; the medications incur financial cost; and, longer duration of therapy promotes the development of antibiotic-resistant pathogens. There are few studies that have directly compared different durations of treatment for complicated soft tissue infections (and none with DFIs), but most prospective studies of antibiotic therapy for soft tissue DFIs have shown that 1–2 weeks of treatment is sufficient. Somewhat more prolonged therapy may be appropriate in the rare DFI that is accompanied by bacteremia. The main indication for a long duration of antibiotic therapy for DFI is treatment of infected bone. Based largely on studies of animal models and clinical experience, most authorities suggest treating osteomyelitis for 4–6 weeks [10]. Despite much discussion of 'bone penetration' of various antibiotics, few data support that this is a key factor in the effectiveness of treating osteomyelitis. Many clinicians treat patients with diabetic foot osteomyelitis who do not undergo surgical resection of bone for considerably longer (3 months, or more), based on experience from retrospective case series [11,12]. When all of the infected and necrotic bone has been surgically removed, a shorter duration of therapy (sometimes as little as a few days) is usually sufficient. A recent small, randomized controlled trial demonstrated that there is no benefit to treating diabetic foot osteomyelitis for more than 6 weeks [13].

The pre-antibiotic era

Why is there such concern about over-prescribing antibiotics? In brief, this practice is driving a growing crisis of resistance of bacteria to these agents. This problem has become so widespread that we are at risk of having no effective antibiotic treatment for many common human

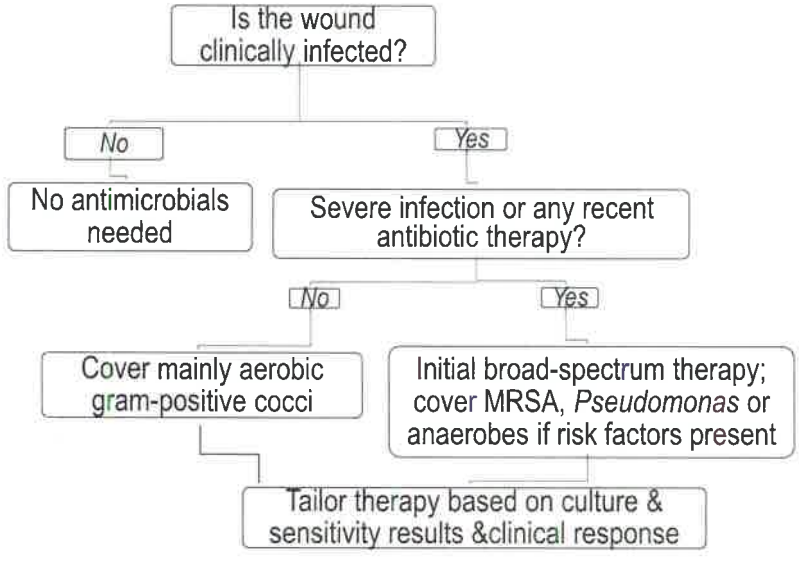

Figure 1. Simplified approach to antibiotic therapy for diabetic foot infection. MRSA, methicillin-resistant *Staphylococcus aureus*

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infections, among which DFIs are high on the list. We can obtain an idea of this scenario by looking back to the pre-antibiotic era. Data from the US Centers for Diseases Control and Prevention show that in 1900 the death rate in the United States was 1100/100 000 and infections of various types caused 52.7% of all deaths; in 2010 the death rate had fallen to <600/100 000 with only 2.7% caused by infections (http://www.cdc.gov/nchs/nvss/mortality_tables.htm). Prior to the availability of sulfa drugs in the mid-1930s, and penicillin in the early 1940s, there were no effective treatments for DFI other than amputation. One case series published in 1939 concerning 84 patients who had what was then called 'diabetic gangrene' showed that after lower extremity amputation (usually at the trans-femur level, for fear of continued spread of infection) the morality rate was 10.4% [14]. Two other cases series published in the late 1940s, one with 140 patients [15] and the other with 1036 patients [16], compared outcomes before and after the availability of penicillin (and sulfonamides). Each reported that the amputation rate dropped from about 70% to about 30% and the mortality rates from about 9% to about 4%. Henry Connor, a highly respected physician with an interest in the history of foot complications in diabetes, opined that after the introduction of insulin (in 1922) the next major advance in treating diabetic foot complications was antibiotic therapy. He noted that in addition to lowering mortality, antibiotic treatment allowed for more limb-sparing surgery (usually below knee or lower) and made primary closure with sutures a safer option [17].

The antibiotic era

Today, we have numerous antibiotic agents for treating DFIs, both by the oral and parenteral routes (Table 1), many of which have demonstrated efficacy in studies of treatment of DFIs. This issue of *Diabetes/Metabolism Research and Reviews* contains a systematic review of treatments for diabetic foot infections that is an update (adding seven new studies) of one published in 2012 [18]. In addition, a Cochrane systematic review of systemic antibiotic therapy for diabetic foot infections has just been published [19]. The authors found 20 randomized controlled trials, with a total of 3791 patients that met their inclusion criteria; six of the studies concerned fluoroquinolone agents, four of carbapenems, three of anti-pseudomonal penicillins, two of cephalosporins, one of broad-spectrum penicillins and four of other antibiotics. The studies were generally of low quality: only half were blinded, only a third had concealed randomization, and a biopharmaceutical company sponsored 90%. Overall, they found that most of the newer antibiotic agents studied were non-inferior to standard antibiotic drugs, and there were no consistent differences in adverse effects. Thus, no one antibiotic or regimen has emerged as an agent of choice (although results with tigecycline were worse than those with ertapenem in one large trial [20]). While there are many topically applied antiseptics (including silver and iodide products) and some topical antibiotics, there are few studies upon which to decide when they might be appropriately used [21]. Ongoing investigations are evaluating both new and old topical antimicrobial agents, used either alone or as adjunctive treatment with a systemic antibiotic.

Clinicians should use the currently recommended criteria, while recognizing that they have limitations, to define when a diabetic foot wound is infected and therefore requires antibiotic therapy. They should then select an empiric antibiotic regimen based on the principles discussed previously and be prepared to modify that choice when new clinical or laboratory data become available. Furthermore, it is important to bear in mind that while antibiotics are necessary for treating a DFI, they are not usually sufficient. All patients will need appropriate wound care (debridement, dressings and pressure off-loading) and most will need some surgical interventions. In particular, while it is clear that some cases of diabetic foot osteomyelitis can be cured with antibiotic therapy alone, most require resection of infected and necrotic bone [22]. Several adjunctive treatments (e.g. hyperbaric oxygen therapy, granulocyte-stimulating factors and topical negative pressure therapy) are available but no studies have proven any of these to be useful for treating infection in a diabetic foot.

The 'post-antibiotic' era?

For the past two decades, we have been facing a growing two-pronged crisis regarding antibiotic therapy: rising rates of resistant strains in the face of reduced development of new agents [23]. As noted 70 years ago by Alexander Fleming, the discoverer of penicillin (*New York Times*, June 21 1945), 'the thoughtless person playing with penicillin is morally responsible for the death of the man who succumbs to infection with a penicillin-resistant organism. I hope this evil can be averted'. Unfortunately, his fear, but not his hope, was well founded. A recent study reported that in the United States, healthcare providers prescribed 262.5 million course of antibiotics in the year 2011; that translates to 842 courses per 1000 persons [24]. In both the United States and Europe, an estimated 25 000 deaths a year are now caused by antibiotic-resistant bacteria.

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Table 1. Antibiotics potentially useful for treating diabetic foot infections

Drug	Renal dosing?	MRSA activity?	Class
Oral agents			
Dicloxacillin/flucloxacillin	No	No	Penicillin (semi-synthetic)
Amoxicillin-clavulanate[a]	Yes	No	β-lactam/β-lactamase inhibitor
Cephalexin[a]	Yes	No	Cephalosporin (1st generation)
Cefdinir	Yes	No	Cephalosporin (2nd generation)
Ciprofloxacin/levofloxacin/moxifloxacin[a]	Yes	No	Fluoroquinolones
Clindamycin[ab]	No	+/–	Lincosamide
TMP/SMX[c]	Yes	+	Folate antagonists
Doxycycline[c]	No	+	Tetracycline
Linezolid[ac]	No	+	Oxazolidinone
Parenteral agents			
Ampicillin-sulbactam[ad]	Yes	No	β-lactam/β-lactamase inhibitor
Piperacillin-tazobactam[ad]	Yes	No	β-lactam/β-lactamase inhibitor
Gentamicin	Yes	No	Aminoglycoside
Imipenem-cilastatin, meropenem[ad]	Yes	No	Carbapenem (group 2)
Ertapenem[abd]	Yes	No	Carbapenem (group 1)
Levofloxacin/ciprofloxacin/moxifloxacin[a]	No	No	Fluoroquinolones
Clindamycin[bd]	No	Some	Lincosamide
Tigecycline[¶a d]	No	Yes	Glycylcycline
Vancomycin[¶#]	Yes	Yes	Glycopeptide
Linezolid[b¶#]	No	Yes	Oxazolidinone
Daptomycin[a¶b]	Yes	Yes	Cyclic lipopeptide
Ceftaroline[ac]	No	Yes	Cephalosporin (5th generation)

Note:
MRSA, methicillin-resistant *Staphylococcus aureus*; TMP/SMX, trimethoprim/sulfamethoxazole.
Renal dosing: may require adjustment of the dose in a patient with renal impairment.
[a]Used in published trials of treatment of diabetic foot infections.
[b]Suspect inducible clindamycin resistance resistant to erythromycin (D-test).
[c]Active against community-associated methicillin-resistant *Staphylococcu aureus*.
[d]Activity against most *Bacteroides fragilis*.
[#]Anaerobic and gram-negative activity lacking. Use in combination for mixed infections.
[¶]Healthcare-associated MRSA and community-acquired MRSA activity.
Modified from Reference [31].

It is crucial for both medical professionals and patients to recognize that antibiotics are not like other medications. Antibiotic agents are responsible for more lives saved than any other kind of drug – an estimated 200 million for penicillin alone. They are also used for both humans and animals, with the latter actually accounting for the larger share. Antibiotics not only treat infections, but their availability for prophylaxis and therapy have allowed for new life-saving procedures that would not otherwise be possible, such as prosthetic joint surgery and cancer chemotherapy. Unfortunately, antibiotics also differ from most medications in other ways. The more they are used, the less effective they become. Analogous to the 'tragedy of the commons', use of this precious but limited resource by one person can reduce its effectiveness for many others. With this in mind, perhaps clinicians can think about the three simple principles that I have summarized as the 'ABX' approach (Figure 2).

It has now become apparent that all antibiotics are destined to become ineffective over time. After billions of years of evolution, microbes have likely invented antibiotics against every biochemical target and resistance mechanisms to protect those targets. Undoubtedly, resistance already exists to antibiotic agents that we have not yet discovered or invented. And yet, biopharmaceutical companies have drastically decreased efforts to discover or develop new antibiotic agents, largely because these are less profitable than drugs that are taken daily for many years. There were no new classes of antibiotic agents approved between 1962 and 2000, and only two new classes since then [25]. As if this were not enough of a problem, there have recently been problems with shortages of licensed antibiotic agents that we expect to have available [26]. Between 2001 and 2013, there were shortages of 148 antibacterial drugs in the United States, each for a mean duration of 7.5 months. The main known reasons were manufacturing issues and supply/demand problems. In this setting, it is not surprising that many noted medical authorities and top political leaders, including Presidents and Prime Ministers, have come to understand the gravity of the situation and called for urgent action on medical, business and legislative fronts.

Fortunately, there are actions we as clinicians can, indeed must, take to slow down, and perhaps even stave off, the apocalyptic vision of a post-antibiotic era. We must avoid using antibiotics for clinically uninfected wounds, while for infected wounds, we must use the most narrowly focused treatment for the shortest duration possible.

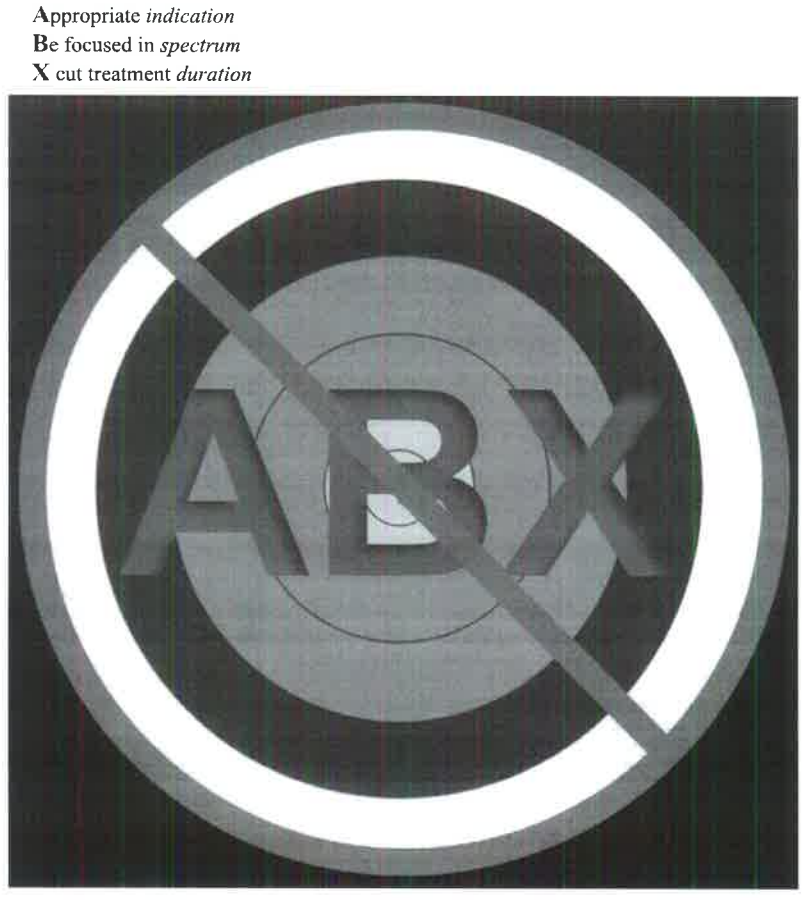

Figure 2. Targeting optimal antibiotic therapy: think 'ABX'. Appropriate *indication*, Be focused in *spectrum*, X-cut treatment *duration*

Antimicrobial stewardship programmes have been effective in improving use of these agents. A recent international survey found that developing a stewardship programme was associated with reductions in 96% of hospitals for inappropriate prescribing, 86% for broad-spectrum antibiotic use, 80% for antibiotic expenditure, 71% for healthcare-acquired infections, 65% for length of stay or mortality and 58% for bacterial resistance [23]. Furthermore, new rapid molecular diagnostic techniques have allowed clinicians to more quickly know which patients require antibiotics and the best ones to select. By now, all clinicians and most well-informed patients are aware of the problem of antibiotic resistance. We certainly need to continue the critical, traditional antibiotic stewardship efforts, including education, restrictions, de-escalation and electronic reminders. But, we also need new ideas. Further education or haranguing is unlikely to reduce inappropriate patient requests, or clinician prescribing of unneeded antibiotic therapy. What does appear to work, however, is 'nudging' improved clinician and patient behaviour by what has been termed 'antibiotic judo', such as simple, public commitments to prescribe antibiotics wisely [27].

On the bright side, there have been some novel approaches to bringing new antimicrobial treatments to market. For example, a remarkable recent discovery has been made about new ways of finding antibiotics from an old source: the soil. This was where most antibiotics were found in the mid-twentieth century and where the uncultured bacteria that comprise ~99% of the species are an untapped potential source of new antimicrobials. Ling and colleagues conducted a remarkable series of experiments with an 'iChip' dipped in a suspension of cells in molten agar that holds growing organisms, which is then placed back in the soil from which they were obtained [28]. Among thousands of potential compounds that they isolated one, named teixobactin, is a highly promising agent active against most gram-positive bacteria by a unique mechanism. This method suggests that we have a new pathway to developing antibiotics that will be slow to develop resistance. Another new development is actually a return to an old treatment – bacteriophages.

These viruses that kill bacteria, discovered 100 years ago, were used clinically until supplanted in most countries by antibiotics. In several Eastern European countries, however, they continue to be used with good results. A recent study from Portugal characterized five bacteriophages found to have antimicrobial activity against both planktonic and biofilm isolates of *S. aureus*, *P. aeruginosa* and *Acinetobacter baumannii* strains from DFIs [29]. This method, and other new techniques, is currently being explored in several countries. While these new methods and discoveries are welcome, they will not overcome the problem of excessive and inappropriate use of antibiotic agents.

Conclusions

Diabetic foot infections can be devastating, often eventuating in hospitalization and occasionally a lower extremity amputation. Over the past three decades, studies have provided data with which evidence-based guidelines (like those in this issue) were developed. These have used a methodical approach to evaluate the available evidence on determining which diabetic foot wounds are infected, how to culture these wounds, what local care and surgical procedures are most appropriate and how to approach providing optimal antibiotic therapy. Using these principles has led to markedly improved outcomes for patients with a DFI [30]. But, problems with excessive, and inappropriate, use of antibiotic therapy for diabetic foot wounds persist. By targeting therapy on the basis of properly obtained culture specimens, constraining the spectrum to isolated pathogens and curtailing the duration of treatment, we can help reduce the current serious problem of antibiotic resistance. This approach, combined with recent and future innovative technologies, may help us at least delay the coming of the 'post-antibiotic era'.

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