Diagnosing and Treating Diabetic Foot Infections

Diyabetik Ayak İnfeksiyonlarının Tanı ve Tedavisi

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Abstract

Persons with diabetes often develop foot wounds, which frequently become infected. Infections typically involve soft tissues at first, but can spread to underlying bone. These infections cause considerable morbidity and are often the proximate cause of lower extremity amputation. Many studies in the past few years have improved knowledge of the most appropriate ways to diagnose and treat diabetic foot infections. This review presents information gathered from a comprehensive, ongoing surveillance of the literature (published and abstracts) over the past 5 years. Prospective studies have now defined the epidemiology of diabetic foot infections, as well as validated methods to score and classify the wounds. Several recently published guidelines can assist clinicians in managing these infections. The etiologic agents of infection have been well-defined, and these can be anticipated by epidemiological and clinical clues. Of particular concern is that the prevalence of multidrug-resistance pathogens (especially methicillin-resistant *Staphylococcus aureus*) is growing. Molecular methods offer great promise for quicker and more sensitive diagnosis of infection. New antimicrobial agents, both systemic and topical, as well as novel local treatments, have been shown to be effective in various studies. Improved methods of deploying older agents have added to the variety of treatment approaches now available. Several adjunctive treatments may benefit some patients but their role is as yet unclear. Recent analyses have provided guidance on managing diabetic foot osteomyelitis. While there is much yet to learn about how to most cost-effectively diagnose and treat diabetic foot infections the main effort is now to disseminate the available information and facilitate employing the evidence-based guideline recommendations.
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Key Words: Diabetic foot infection, diagnosis of infection, antimicrobial therapy, microbiology.

Özet

Diyabetik kişilerde ayak yaraları sık görülür ve bunlar sık sık infekte olur. Yumuşak dokuda başlayan infeksiyon, alttaki kemiğe de ilerleyebilir. Bu infeksiyonlar, önemli ölçüde morbiditeye yol açarlar ve alt ekstremite ampütasyonunun da en sık nedenidir. Son yıllardaki çalışmalar, diyabetik ayak infeksiyonlarının tanı ve tedavisinde en uygun yolların neler olduğunu göstermiştir. Bu derlemede son beş yıldaki literatürün (yayımlanmış ve özet halindeki) geniş bir biçimde gözden geçirilmesiyle elde edilen bilgiler sunulmaktadır. İleriye dönük çalışmalarla diyabetik ayak infeksiyonlarının epidemiyolojisi tanımlandığı gibi yaraları derecelendiren ve sınıflandıran yöntemlerin geçerliliği de ortaya konulmuştur. Bu infeksiyonların yönetimi için klinisyenlere yardımcı olmak üzere son yıllarda yayımlanmış birkaç kılavuz vardır. İnfeksiyonun etyolojik etkenlerinin neler olduğu iyi tanımlanmıştır; epidemiyolojik ve klinik ipuçları da bunların kestirilmesini sağlayabilir. Çoğul dirençli patojenlerin (özellikle metisiline dirençli *Staphylococcus aureus*'un) prevalansındaki artış bir kaygı kaynağıdır. Moleküler yöntemler infeksiyonun daha hızlı ve daha duyarlı tanısı için umut vermektedir. Çeşitli çalışmalarla yeni lokal tedaviler kadar gerek sistemik gerekse topik olarak kullanılan yeni antimikrobik ajanların da etkili olduğu gösterilmiştir. Var olan tedavi yaklaşımlarına daha eski ajanların kullanıldığı ileri yöntemler eklemiştir. Birtakım yardımcı tedaviler bazı hastalarda yararlı olabilirse de rolleri henüz kesin değildir. Son analizler diyabetik ayak osteomyelitinin yönetimi için yol gösterici olmuştur. Diyabetik ayak infeksiyonlarının tanı ve tedavisinin en maliyet etkin olarak nasıl yapılacağına ilişkin öğrenilecek daha pek çok şey olmakla birlikte, var olan bilgiyi yaymak ve kanıta dayalı kılavuz önerilerinin uygulanmasını kolaylaştırmak için çaba gösterilmesi gerekmektedir.
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Anahtar Sözcükler: Diyabetik ayak infeksiyonu, infeksiyon tanısı, antimikrobik tedavi, mikrobiyoloji.

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Introduction

Foot wounds are a common and growing problem in persons with diabetes (1). Many factors may predispose to these foot wounds (Table 1), but they are generally a consequence of various types of trauma to an insensate (and often ischemic) foot. Once the protective cutaneous barrier is breached, skin flora can gain access to the subcutaneous tissue, proliferate, and cause the host inflammatory response we classify as infection (2). Infection of the soft tissue can then spread contiguously to underlying bone, causing osteomyelitis. The occurrence of bone infection substantially reduces the likelihood of a good outcome. Foot infections are now the most frequent reason for diabetes-related hospitalizations, and are the major proximate cause of lower limb amputation in persons with diabetes (Figure 1). Since amputation is associated with about a 50% 5-year mortality, providing optimal care for patients with a diabetic foot infection (DFI) is crucial (3). Fortunately, active research in the field of DFIs has allowed several groups to develop evidence-based guidelines for caring for DFIs.

The increase in investigative activity in this field was likely catalyzed by the publication of two sets of guidelines specifically concerning DFIs. The first, a product of a consensus meeting of the International Working Group on the Diabetic Foot (IWGDF) was published in 2004 (4). The second was released soon thereafter by a committee designated by the Infectious Diseases Society of America (IDSA) (2). More recently, a set of guidelines was published by French-speaking experts, with a shorter version in English (5). Other recent guidelines have also addressed infection as part of a larger overview of diabetic foot complications (5-7). Finally, a Progress Report on Diagnosing and Treating Diabetic Foot Osteomyelitis was presented at the 5th International Symposium on the Diabetic Foot. These guidelines have largely offered similar sets of recommendations, helping to codify an approach to diagnosing and treating DFIs.

Guidelines and Classifications

Managing a DFI first requires that the clinician properly evaluate the problem; this progresses from a general evaluation of the whole patient, to examining the affected limb, then the foot, and finally the specific wound (Table 2). An important aspect of the IWGDF and IDSA guidelines is that they developed criteria by which to classify the severity of a DFI (Table 3). This classification helps clinicians recognize severe infections, which may require hospitalization, broad-spectrum and parenteral antibiotic therapy, or urgent diagnostic or surgical interventions. Generally, mild infections are relatively superficial and limited, moderate infections involve deeper tissues and severe infections are accompanied by systemic signs or symptoms of infection or metabolic perturbations. The epidemiology of foot wounds and approximate distribution of these infections in persons with diabetes is shown in Figure 2.

Using the data from a prospective study of patients who developed a foot infection, Lavery *et al* (8) were able to validate the IDSA classification system. They found a statistically significant trend toward an increased risk for lower extremity amputation, higher-level amputation, and a higher rate of lower extremity-related hospitalization with increasing infection severity. Another newly reported finding is that one can predict the outcome of infection by the presence and severity of selected clinical and laboratory findings (9). Among 402 clinically evaluable patients enrolled in a prospective antibiotic treatment study, baseline factors significantly associated by univariate analysis with treatment failure were "severe" (*versus* "moderate") University of Texas (UT) wound grade; elevated white blood cell count, C-reactive protein or erythrocyte sedimentation rate; high wound severity score; hospitalization for treatment; low serum albumin; male sex; and, skin temperature of affected foot >10°C above that of unaffected foot (9). By multivariate logistic regression only severe UT wound grade and elevated white blood cell count remained statistically significant predictors. Clinical failure rates were 46% for patients with both risk factors compared with 10% for patients with no risk factors and 17% for patients with one risk factor. Increased white blood cell count and severe UT wound grade at baseline, but not other features, were significant independent and additive risk factors for clinical failure in patients treated for a DFI (9).

Wound Scoring System

Another advance has been the development and validation of a DFI wound scoring system. Does a DFI wound score correlate with the clinical response to antibiotic treatment? Lipsky *et al* (10-13) formulated a preliminary version of this score for use in two previous studies of antibiotic therapy for

Table 1. Risk Factors for Foot Ulceration and Infection (Modified from Reference 2)

Risk Factor	Mechanism Leading to Ulceration, Impaired Wound Healing or Infection
Peripheral sensory neuropathy	Loss of protective sensation (e.g., repetitive shear-type stress leading to ulceration)
Peripheral motor neuropathy	Abnormal foot anatomy and biomechanics resulting in excess pressure
Peripheral autonomic neuropathy	Impaired sweating leading to dry, cracked skin
Arterial insufficiency	Diminished delivery of nutrients, oxygen, neutrophils, etc. leading to impaired wound healing and clearance of infection
Hyperglycemia	Immune system (e.g., neutrophil) dysfunction and excess collagen cross-linking
Patient disability or non-adherence	Reduced vision (unable to inspect feet), prior amputation, lack of regular follow-up with medical care, poor hygiene, inappropriate footwear

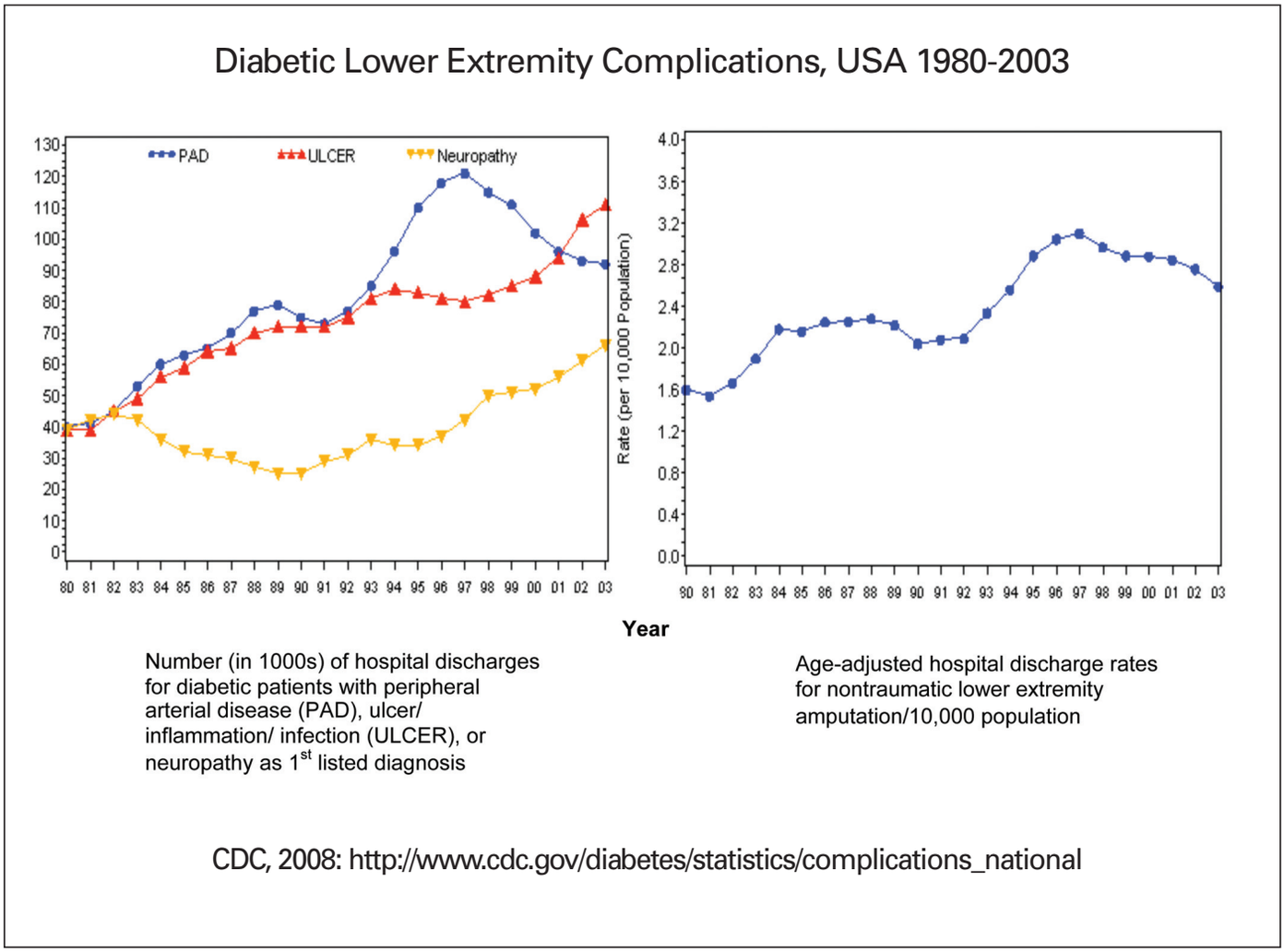

Figure 1. Incidence of foot complications, foot-related hospitalizations and lower extremity amputations in persons with diabetes.

Table 2. Approach to Evaluating a Diabetic Patient with a Foot Wound (Modified from Reference 2)

Evaluating a Diabetic Patient with a Foot Wound
• Check for sensation (monofilament)
• Check for circulation (pulses, Dopplers)
• Cleanse and debride ulcer
• Evaluate for infection
• Probe wound (foreign bodies, bone?)
• Consider need for surgery
• Prescribe antibiotics if infected
• Adequately offload pressure; prescribe proper dressing
• Educate about secondary prevention
• Set up appropriate follow-up

DFIs then used a slightly modified version for the SIDESTEP antibiotic study. Investigators noted the presence of drainage (purulent or non-purulent), then graded any erythema, induration, tenderness, pain, and local warmth for severity. This score, combined with measurements of wound size and depth, gave a total wound score. Among 373 evaluable patients, a higher score was associated with a significantly reduced infection cure rate (14). This scoring system thus appears to offer clinicians an objective way to classify the severity of an infected diabetic foot wound, and this correlates with clinical outcome.

Epidemiology

The results of two recent studies have provided an important advance in this field in finally providing some prospective data on the occurrence of DFIs. Lavery *et al* (15) reported the results of following 1666 diabetic persons in a health maintenance organization in Texas for a mean of just over two years. Despite the fact that the patients were screened for foot problems both at enrollment and regularly thereafter, and educated in how to prevent foot problems, 151 (9%) developed 199 foot infections. All but one infection occurred in the setting of a wound or penetrating injury; most involved only the soft tissue but 20% had bone culture-proven osteomyelitis. Those who developed a foot infection had a dramatically higher risk of hospitalization and lower extremity amputation. Significant independent risk factors for foot

Table 3. Clinical Classification Schemes Proposed by the Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (PEDIS system) for a Foot Infection in a Person with Diabetes

Clinical Manifestations of Wound	IDSA	PEDIS*
No purulence or evidence of inflammation (i.e., erythema, pain, tenderness, warmth or induration)	Uninfected	1
Infected (≥2 of above) but any erythema extends ≤2 cm around ulcer & infection limited to skin/superficial subcutaneous tissues. No local complications or systemic illness	Mild	2
Infected patient who is systemically well & stable metabolically but has at least one of following: cellulitis >2 cm; lymphangitis; spread beneath fascia; deep tissue abscess; gangrene; muscle, tendon, joint or bone involved	Moderate	3
Infected patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis)	Severe	4

*PEDIS: **P**erfusion, **E**xtent/size, **D**epth/tissue loss, **I**nfection and **S**ensation

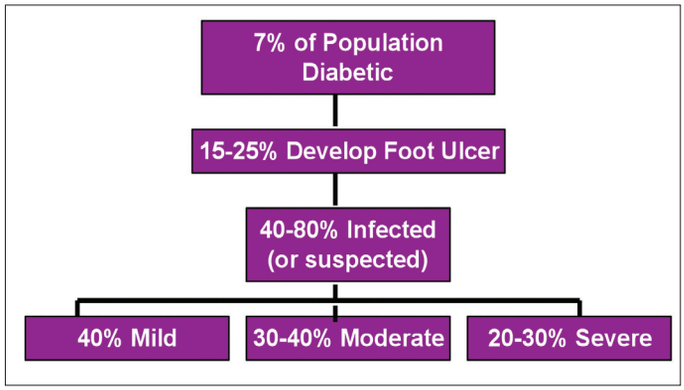

Figure 2. Epidemiology of diabetic foot infections.

infection from a multivariate analysis included wounds that penetrated to bone, had a duration >30 days, were recurrent or associated with a traumatic etiology, and the presence of peripheral vascular disease (15).

Another report was published by the Eurodiale study group on data from diabetic patients with a foot ulcer in 14 European hospitals in ten countries (16). Among 1229 patients, 58% had a clinically infected wound. The severity of diabetic foot ulcers at presentation was greater than previously reported, and one-third had peripheral arterial disease in addition to infection. The majority of foot ulcers were non-plantar, especially in patients with severe disease, and serious co-morbidity increased with the severity of foot disease (16). Thus, DFIs are common, typically occur in a traumatic wound, affect the majority of foot ulcers, and are associated with limb ischemia. In a follow-up study these investigators reported that after 1 year of follow-up, 23% of the patients had not healed their diabetic foot wound (17). Independent baseline predictors of non-healing were older age, male sex, the presence of heart failure or end-stage renal disease, the inability to stand or walk without help, a larger ulcer size, the presence of peripheral neuropathy and peripheral arterial disease (PAD). Infection was a specific predictor of non-healing only in patients with vasculopathy. Because predictors of diabetic foot wound healing differed between patients with and without PAD, they suggested that these be defined as two separate disease states. Of note is that the adverse effect of infection on healing was confined to patients with PAD; this needs further investigation (17). Another recent prospective study from Singapore found that among 192 diabetic patients hospitalized for a foot complication, the most common conditions included gangrene (31.7%), infection (abscess, osteomyelitis) (28.7%), ulcer (27.7%), cellulitis (6.4%), and necrotizing fasciitis (3.5%) (18). The only risk factors for limb amputation found to be statistically significant by stepwise logistic regression analysis were peripheral vascular disease and infection.

Microbiology

In order to select the most appropriate antibiotic therapy for a DFI one must know the causative pathogens and their antibiotic susceptibilities. This requires obtaining specimens for culture that are properly collected (Table 4). Many studies have reported the causative organisms in a series of patients with a DFI. The results of these studies vary with the severity of the infection, whether or not the patients had recently received antibiotic therapy, as well as with the quality of the culture procedures used. Specific pathogens are more frequently isolated with certain clinical syndromes, as shown in Table 5. Although several studies have demonstrated the superiority of deep (preferably tissue) specimens over superficial swabs, especially for bone infections, most clinicians persist in sending wound swabs (19-23). In a recent large, prospective antibiotic trial most specimens were obtained with proper technique and sent to a research laboratory for optimal microbiological evaluation (24). Among 427 positive cultures, 84% were polymicrobial; almost half grew only aerobes, but 47% had both aerobes and anaerobes. There was an average of 2.7 organisms per aerobic culture and 2.3 per anaerobic culture. As has been found in most other studies, the predominant aerobic organisms (in descending order) were *Staphylococcus aureus*, coagulase-negative staphylococci, *Streptococcus* species, *Enterococcus* species, *Corynebacterium* species, *Enterobacteriaceae*, and *Pseudomonas aeruginosa*. The predominant anaerobes were Gram-positive cocci, *Prevotella* species, *Porphyromonas* species and *Bacteroides fragilis* group. Of note is that the majority of patients

with methicillin-resistant *S. aureus* (MRSA), *S. epidermidis* or *P. aeruginosa* had a mixed infection (24). These data support the results of many other studies that have found that aerobic Gram-positive cocci (particularly staphylococci) are the most frequent causes of DFIs, but that mixed infections, with aerobic Gram-negative bacilli or obligate anaerobes, are common as well (25).

Antibiotic-Resistant Pathogens

One major change in the causative organisms of DFIs in the past few years is the increasing frequency of isolation of MRSA (26-28). Several studies have found that 30-50% of *S. aureus* isolates from diabetic foot ulcers are methicillin (oxacillin) resistant (29,30). This is noteworthy because MRSA requires specifically targeted antibiotic therapy. Because the rate of MRSA isolation varies considerably from one location to another it is key that clinicians be aware of their local resistance situation. In one report the prevalence of MRSA was significantly higher in patients with clinically infected foot ulcers than in those with just colonization (31). Interestingly, in this study MRSA infection or colonization was not associated with previously reported predisposing factors, e.g., prior hospitalization or use of antibiotics. Isolating MRSA from a diabetic foot wound is related to nasal colonization with the organism (27). Presumably, eradication of colonization may require eliminating the nasal colonization. Some studies have also reported increasing frequency of antibiotic-resistant (including extended-spectrum β-lactamase producing) Gram-negative organisms, particularly *Pseudomonas* species (28,32,33). In one study of 102 diabetic patients with a foot wound, the significant risk factors for having a multidrug-resistant diabetic foot pathogen were: previous antibiotic therapy and its duration, frequency of hospitalization for the same wound, duration of hospital stay and the presence of osteomyelitis (34).

Table 4. Recommendations for Collection of Appropriate Specimens for Culture From Diabetic Foot Wounds (Modified from Reference 2)

Do
• Cleanse and debride wound before obtaining specimen(s) for culture
• Obtain tissue specimen for culture by scraping with a sterile scalpel or dermal curette (curettage) or biopsy from the base of a debrided ulcer
• Aspirate any purulent secretions using sterile needle/syringe
• Promptly send specimens for culture in sterile container or appropriate transport media for aerobic and anaerobic culture
Do Not
• Culture clinically uninfected lesions, unless for epidemiological studies
• Obtain specimen for culture without first cleansing or debriding the wound
• Obtain specimen for culture by swabbing the wound or wound drainage

Rapid Diagnostic Methods

Wound cultures may not adequately identify pathogens, especially when they are not obtained or processed correctly or when the patient is on antimicrobial therapy. Even when pathogens grow, it takes at least 24-48 hours to identify them and obtain antibiotic sensitivity results. One method of getting rapid information about the likely causative organisms in a DFI is to do a Gram-stained smear of tissue from the wound. Newer technologies may enable rapid identification of causative pathogens (35). One technique, the polymerase chain reaction (PCR) assay, has been shown to be effective at

Table 5. Pathogens Associated with Specific Diabetic Foot Infection Syndromes (Modified from Reference 2)

Diabetic Foot Infection Syndrome	Pathogen
Cellulitis without ulceration	β-hemolytic streptococci (especially group B) and *Staphylococcus aureus*
Ulcer or wound, recently developed and no prior antibiotic treatment	*S. aureus* and β-hemolytic streptococci
Ulcer or wound, chronic or recent antibiotic treatment	Usually polymicrobial – *S. aureus* and β-hemolytic streptococci plus *Enterobacteriaceae*. Enterococci if previous cephalosporin therapy.
Ulcer or wound, prior hydrotherapy or green-blue colored drainage	*Pseudomonas aeruginosa* (often in combination with other organisms)
Extensive necrosis or gangrene, ischemic limb, feculent odor ("fetid foot")	Polymicrobial – mixed aerobic Gram-positive cocci (including enterococci), *Enterobacteriaceae*, nonfermentative Gram-negative rods, and obligate anaerobes
Healthcare-associated	MRSA; ESBL-producing Gram-negative rods

MRSA: Methicillin-resistant *Staphylococcus aureus*

ESBL: Extended spectrum β-lactamase

identifying many Gram-positive, Gram-negative and anaerobic organisms in various types of wounds. Another potentially useful new diagnostic technology is the oligonucleotide array for detecting various genes, including those coding resistance, toxins and specific species (36). A recent study investigated 72 diabetic patients hospitalized with a foot ulcer who had monomicrobial colonization or infection with *S. aureus*. Few of the clinically uninfected ulcers had virulence genes, while they were present in almost all the infected ulcers (37). The presence of these virulence factors also predicted a worse clinical outcome. Real time PCR may allow clinicians to discriminate infected from colonized wounds, which could help direct antibiotic therapy. It also allows the laboratory to identify the infecting pathogens in hours rather than days, whether or not the patient has been treated with antimicrobials and with far greater sensitivity than standard culture methods (38). Recent studies using techniques such as 16S-based molecular amplifications followed by pyrosequencing, shotgun Sanger sequencing, and denaturing gradient gel electrophoresis have shown the diverse populations of bacteria that occur in the pathogenic biofilms of various chronic wounds, including diabetic foot ulcers (39). These include populations of bacteria that culture methods failed to correctly identify and many that have not been recognized as wound pathogens, indicating the need for improved diagnostic methods.

Imaging Techniques

There have been some new developments in the area of diagnostic imaging of soft tissue and bone infections (40). While MRI has emerged as the preferred imaging modality for DFIs, several new nuclear medicine techniques have been introduced (41,42). These include directly targeting white blood cells by radiolabeling receptors *in vivo*, attempting to target live bacteria with antimicrobial labels, using analogs of natural mammalian antimicrobial agents and targeting fungi with labeled anti-fungal agents (43). Another approach has been to combine standard imaging methods, like labeled leukocyte scans, with positron emission tomography and computed tomography (PET/CT) scans (44-46). This offers correlated acquisition of metabolic and anatomic data, providing high diagnostic accuracy. Some authorities believe that PET/CT scans are likely to be routinely employed for characterizing, and monitoring patients with suspected and proven DFI (46). Most believe, however, that the proper circumstances in which to currently consider using these and similar methods, and their cost-effectiveness, are as yet unknown.

Treatment

Defining the microbiology of an infection is the prelude to deciding on the most appropriate antibiotic treatment regimen. In general, while all wounds are colonized with microorganisms, only those that show clinical signs of infection require antimicrobial therapy. Systemic antibiotic therapy should be relatively narrowly targeted when possible, but broader spectrum or specially targeted therapy is often indicated when a patient has a clinically severe infection or is likely to be infected with a resistant pathogen (Figure 3). In the past few years many studies have reported the results of treatments for DFIs (47). These include antimicrobial agents of various types, delivered in different ways, as well as several kinds of adjunctive treatments. Unfortunately, there is still little to no evidence to support the effectiveness of many treatments. In fact, a recent systematic review of the effectiveness of antimicrobial treatments for diabetic foot ulcers summarized the results of papers published up until November 2002 (48). The authors, after reviewing the 23 eligible randomized or controlled clinical trials, concluded that "the evidence is too weak to recommend any particular antimicrobial agent. Large studies are need of the effectiveness and cost-effectiveness of antimicrobial interventions." (49). Some of the studies that have been published in the 4 years since this review are shown below.

Topical and Local Antimicrobials

Topical antimicrobial therapy continues to be an appealing method for treating infected wounds. Several new silver-based products have been marketed, but a recent Cochrane systematic review that examined papers published through 2004 concluded that, "despite the widespread use of dressings and topical agents containing silver for the treatment of diabetic foot ulcers, no randomised trials or controlled clinical trials exist that evaluate their clinical effectiveness." (49). Similarly, there are few studies of the efficacy (or safety) of topical iodides in treating DFIs (50). Investigational topical agents for treating DFI include antimicrobial peptides, such as pexiganan (51) and superoxidized water solutions, such as Dermacyn® (52-54). Studies to determine the usefulness of several of these new agents are currently being developed.

Investigators have tried a variety of antibiotic delivery mechanisms to treat open diabetic foot wounds. These include biodegradable materials, such as vancomycin impregnated calcium sulfate beads and gentamicin incorporated into collagen (55-57). These devices can deliver high local antibiotic concentrations, for a sustained period of time with minimal systemic levels. Another new method of instilling

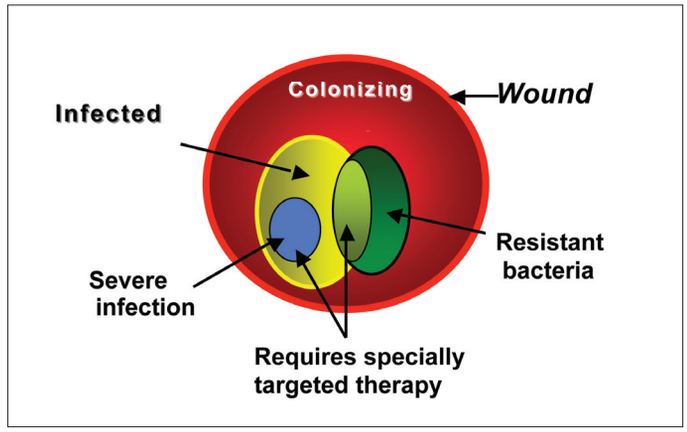

Figure 3. Approach to selecting an empiric antibiotic regimen for a patient with a diabetic foot wound. Treat only clinically infected (not colonized) wounds. It is generally preferable to use a relatively narrow-spectrum antibiotic regimen, but certain situations warrant specially selected or broader-spectrum therapy.

antibiotics into a wound is designed to work in conjunction with the vacuum assisted closure device (VAC) (58). This device can be applied within 24 hours after a wound has been adequately surgically debrided, and usually in conjunction with systemic antibiotic therapy. Another novel method of treating infected foot ulcers is the so-called Biogun (59,60). This device ionizes molecular oxygen and generates superoxide radical anions (O_2^-) that have a bactericidal effect against microorganisms. In a pilot study of 15 patients with MRSA colonization of a diabetic foot ulcer this device eradicated the organism from 60%. Honey, a topical agent that has been used for many years, has recently been promoted for treating MRSA infections, and the American Academy of Family Physicians is co-sponsoring a randomized controlled trial for treating diabetic foot ulcers. Another example of an older approach being resurrected in these times of increasing antibiotic resistance is bacteriophage therapy. These viruses that kill bacteria were discovered 90 years ago, but fell out of use in most parts of the world after the discovery of antibiotics (61). One review of over 1300 patients with infections caused by multiresistant bacteria who were treated with specific bacteriophages reported full recovery in 85% and transient improvement in another 11% (62). Yet another long-used form of biotherapy, maggot debridement, has also been found to be effective in eradicating MRSA colonization of diabetic foot ulcers (63). Determining which if any of these old or new remedies may prove useful in treating DFIs will require proper controlled trials.

Systemic Antimicrobials

Several studies of systemic antibiotic therapy of DFIs have been published in the past few years. In light of the concern for MRSA infections, one study compared linezolid, a newly developed oxazolidinone antibiotic active against almost all Gram-positive organisms, against an aminopenicillin/β-lactamase inhibitor (10). Although other specified antibiotics that are 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. Nevertheless, linezolid was at least as effective as the broader-spectrum agent, with a similar safety profile. In another study of a subset of patients with a DFI, daptomycin, another new anti-MRSA drug, was compared to vancomycin (for patients with MRSA infection) or semi-synthetic penicillin (for patients with a methicillin-sensitive infection) (64). The clinical and microbiological efficacy and safety were similar for all three arms of the study. More recently, a new once-daily dosed class 1 carbapenem antibiotic, ertapenem, was compared with the somewhat broader-spectrum agent piperacillin/tazobactam in a large group of patients with a DFI (13). Again, the clinical and microbiological outcomes and safety profile were similar for the two study drugs. Finally, in yet another study of patients with DFIs, moxifloxacin, a broad-spectrum fluoroquinolone, had comparable outcomes to piperacillin/tazobactam (IV) or amoxicillin/clavulanate (orally) (24). While these studies do not allow us to select any one agent as preferable to others, they do demonstrate the effectiveness of several new antibiotics. On the basis of these studies, linezolid, ertapenem and piperacillin/tazobactam have been approved by the US FDA specifically for treating DFIs (but not for osteomyelitis).

Multidrug resistance is an increasing problem in isolates from DFIs, especially MRSA and extended-spectrum β-lactamase-producing Gram-negative bacteria. This emergence of drug resistance has led to the development of many new antibiotics (65). A number of investigational antibiotic agents, including ceftobiprole and dalbavancin, appear to be promising for treating DFIs, based on their pharmacological properties and effectiveness *in vitro* against strains of bacteria that were recovered from clinical DFIs (66,67). Of note is that some older agents that were supplanted by newer drugs or were largely discarded because of concerns about toxicity have been used to treat resistant infections. In two reports the now rarely-used polymixin agent colistin (alone or combined with other antimicrobials) was found to be effective in treating a series of diabetic patients with soft tissue or bone infections caused by multidrug-resistant *P. aeruginosa* (68,69). In a similar vein, optimizing how we use available agents can lead to better clinical outcomes. One pharmacokinetic analysis of therapy with oral and parenteral amoxicillin/clavulanate in patients with a DFI found that a reduction in viable bacteria was reached significantly earlier with continuous IV infusion compared with intermittent dosing (70). A recent systematic review looked at randomized controlled trials of DFIs to determine what factors might be associated with treatment failure (71). Among the 18 trials identified, the combined observed treatment failure rate was 23%. Comparing different regimens of antibiotics suggested that carbapenems were associated with fewer treatment failures, while MRSA infections, alone or as part of a polymicrobial infection, were associated with more treatment failures.

Adjunctive Therapies

Finally, several therapies that are not directly antimicrobial have been used in conjunction with antibiotics or other treatments to attempt to improve outcomes in DFIs. Certainly, all patients need supportive therapy, including optimal glycemic control and proper wound dressings, and fluid and electrolyte resuscitation for severely ill patients. Most patients also need some type of surgical procedure, ranging from bedside or clinic debridement, through incision and drainage or operative debridement, to bone resection, revascularization or amputation. Among the more widely used adjunctive treatments is systemic hyperbaric oxygen. It is difficult to interpret the results of the many published case series, but a systematic review of four randomized controlled trials with a total of 147 patients concluded that there was some benefit to the therapy, especially in reducing major amputations (72). The studies are methodologically weak, however, and the one study with a sham treatment arm showed no effect (73). Another expensive new technology is granulocyte colony stimulating factor (G-CSF). A systematic review of the

five published randomized controlled trials with a total of 167 patients found that the various regimens used afforded no improvement in resolving infection but they were associated with significantly fewer operative interventions (including amputations) (74). Additional studies are needed to determine if the substantial resources consumed by these expensive treatments could be better spent on other measures. Of course one additional "adjunctive" measure that is frequently crucial in treating a DFI is surgical debridement and drainage. It is important that this be undertaken by a surgeon with knowledge of the complex anatomy of the foot (Figure 4).

Osteomyelitis

Epidemiology and Pathophysiology

Bone infection of the foot in patients with diabetes generally occurs by contiguous extension from an infected soft tissue wound (75). Thus, virtually all diabetic foot osteomyelitis cases are chronic by the time they are discovered. While foot ischemia may predispose to more severe infections, it is not the primary pathogenic feature for osteomyelitis. Several studies have shown that about 20% of patients presenting with a DFI will have apparent bone involvement, but the prevalence may be over 60% in patients with a limb-threatening infection (76,77). Most often osteomyelitis occurs in a patient with a pre-existing foot wound, and typically the affected bone underlies a neuropathic ulcer. The presence of osteomyelitis lessens the likelihood of successful eradication of a foot infection and, not surprisingly, increases the risk of limb amputation. Osteomyelitis is perhaps the most contentious aspect in the field of DFIs, with only minimal consensus on either how to diagnose or treat this infection (78).

Diagnosis

The first problem encountered in seeing a patient with possible diabetic foot osteomyelitis is making the diagnosis. Clinical signs are highly variable and some patients may have no evidence suggesting underlying bone infection (45,79). Clinical findings suggestive of diabetic foot osteomyelitis include having a soft tissue ulcer that is deep, chronic, or located over a bony prominence, or having a markedly elevated inflammatory marker (ESR, CRP). The "probe to bone" test is also a useful bedside technique for helping to diagnose osteomyelitis (Figure 5). A positive test, i.e., when a sterile metal probe reveals bone (a hard, gritty surface), increases the likelihood of osteomyelitis, while a negative test in a low risk patient markedly decreases the likelihood. Plain radiographs are the first imaging study to consider when osteomyelitis is suspected. In established cases they often show cortical disruption, and sometimes periosteal elevation or pathological fractures. There are two main problems with plain x-rays: they may not show changes in the first two weeks after infection (a lack of sensitivity); and, when changes are apparent they may be caused by non-infectious neuro-osteoarthropathy or Charcot foot (a lack of specificity) (78). To overcome the first problem, many clinicians order nuclear medicine studies, especially bone (and sometimes leukocyte or immunoglobin) scans. While these are more sensitive than x-rays they are rather non-specific. Many studies have shown that the best imaging test, when it is available, for diabetic foot osteomyelitis is magnetic resonance imaging (MRI) (40). Newer techniques, such as positron emission tomography (PET) scans appear promising, but their role is as yet undefined (45,46).

The criterion standard for diagnosing osteomyelitis is a positive culture or (especially in a patient receiving antibiotic therapy) characteristic histopathology (acute or chronic inflammatory cells, or necrosis) from a properly obtained bone specimen (80). The specimen may be obtained at the time of surgical debridement or by percutaneous biopsy. Bone biopsy

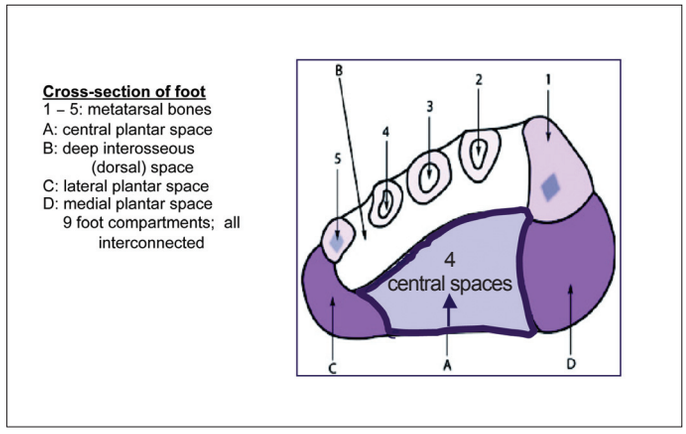

Figure 4. The anatomic compartments of the foot (modified from reference 81).

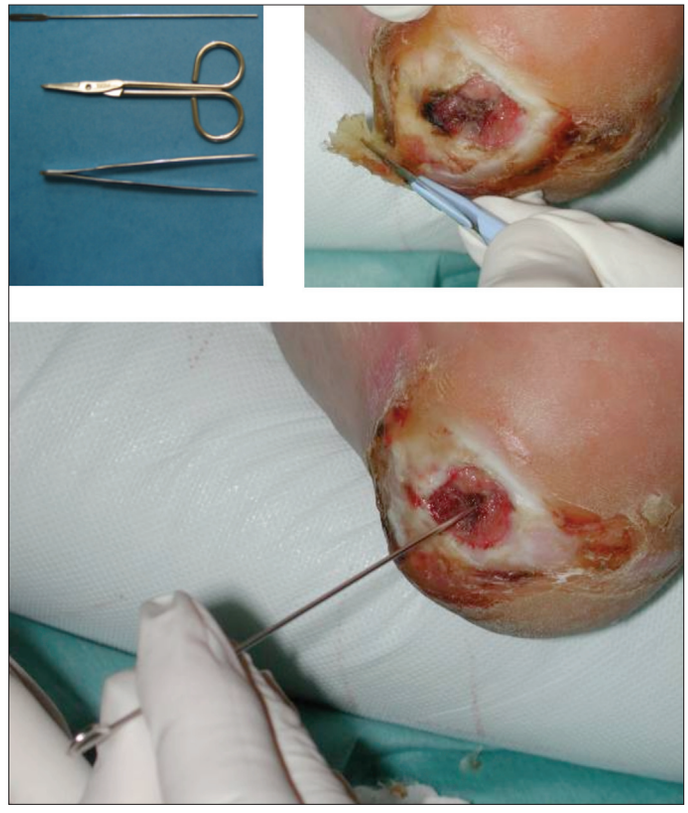

Figure 5. The "probe-to-bone" test for diabetic foot osteomyelitis.
*Note that the wound must first be carefully debrided (preferably with surgical instruments, as shown above) and that the probing should be done with a sterile metal (not wood or plastic) probe.

is usually done under fluoroscopic or computed tomography guidance, is generally simple and safe, and provides more accurate culture results than soft tissue specimens (22). Furthermore, there is some evidence that treatment based on bone culture results is associated with a higher infection remission rate (82). Recently, the International Working Group on the Diabetic Foot proposed consensus criteria for diagnosing diabetic foot osteomyelitis (Table 6 and 7) (83). These criteria remain to be validated in a properly designed trial.

Treatment

The second major problem in dealing with osteomyelitis is the lack of good data upon which to base therapy. The first issue is whether or not the patient needs surgical debridement of necrotic or infected bone. While this has long been advocated, and makes clinical sense, a recent systematic review of the literature found that there are few data to support the need for surgery (83). Urgent surgery may be needed for deep soft tissue infections, but rarely for osteomyelitis, per se. A substantial number of retrospective case series, with a total of almost 600 patients, have shown that antibiotic therapy alone (usually for at least 3 months, often with fluoroquinolone agents) can induce remission of apparent osteomyelitis in about 60% of patients (84). One prospective study found that 82% of 113 patients with probable diabetic foot osteomyelitis achieved apparent remission with antibiotic therapy and no surgery (85). Most authorities still believe that it is best to remove necrotic bone, but the available data support a trial of antibiotic therapy if this is not feasible or preferred by patient and provider. There is very little evidence-based information upon which to choose antibiotic therapy for chronic osteomyelitis (86). As to duration of therapy, it should be longer (perhaps 4-6 weeks) in patients in whom infected bone has not been removed, and can be quite short (probably no more than a week) when it has been.

Summary

Much research has led to substantial progress in our understanding how to diagnose and to treat foot infections in patients with diabetes. More investigators are asking and answering key questions in this arena, and the addition of new treatments and refinements of older ones have likely improved the outlook for patients with a DFI. Most studies now show that more than 80% of patients with a soft tissue infection and over 60% with osteomyelitis can expect clinical resolution. New guidelines have codified the principles of managing DFIs. The job is now to disseminate this information and facilitate employing the recommendations.

Conflicts of Interest

The author has served as a consultant to or received research funding from: Merck, Pfizer, Wyeth-Ayerst, Bayer, Cubist, Johnson & Johnson (Ortho-McNeill Janssen).

Table 7. Implications of Diagnostic Categories for Diabetic Foot Osteomyelitis (Modified from Reference 83)

Diagnostic Category	Implication for Investigation	Implication for Treatment
Definite (>90% likely)	No further tests except C&S	Should treat
Probable (50-89%)	Confirmatory tests advised	Strongly consider treatment
Possible (10-49%)	Further tests or observation	May treat or observe
Unlikely (<10% likely)	Observation only for osteomyelitis	Need not treat

C&S: Culture and sensitivity

Table 6. Proposed Consensus Criteria for Diagnosing Osteomyelitis of the Foot in a Patient with Diabetes (Modified from Reference 83)

Category	Finding	Combinations
Definite (Any 1 of)	• + Bone culture & histology • Pus in bone at surgery • Detached bone in ulcer • Bony abscess on MRI	2 probable 4 possible 1 probable + 2 possible
Probable (Any 1 of)	• Visible cancellous bone • MRI highly likely • + Bone culture or histology	2 possible
Possible (Any 1 of)	• Cortex erosion on X-ray • MRI compatible • + Probe to bone • Visible cortical bone • ESR>70 mm/h • Chronic, inflamed wound	
Unlikely (Any 1 of)	• Normal MRI • Normal bone scan • Acute ulcer without inflammation, and a normal X-ray	

MRI: Magnetic resonance imaging, ESR: Erythrocyte sedimentation rate

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