Diabetic Foot Infections

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LEARNING OBJECTIVES

1. Distinguish the factors that increase the risk of diabetic foot infections (DFIs) in a patient.
2. Assess the severity and extent of DFI on the basis of clinical tests and findings.
3. Evaluate a patient's risk factors for multidrug-resistant organisms when selecting an appropriate empiric antimicrobial therapy for DFIs.
4. Analyze differences between therapeutic agents in pharmacokinetics and efficacy depending on the severity and extent of DFI.
5. Design an appropriate antimicrobial treatment and monitoring plan for a patient with a DFI with or without osteomyelitis.
6. Develop a plan to prevent diabetic foot ulcers in the patient with diabetes.

ABBREVIATIONS IN THIS CHAPTER

DFI	Diabetic foot infection
DFO	Diabetic foot osteomyelitis
DFU	Diabetic foot ulcer
HBOT	Hyperbaric oxygen therapy
MRSA	Methicillin-resistant Staphylococcus aureus
MSSA	Methicillin-sensitive Staphylococcus aureus
SSTI	Skin and soft tissue infection

Table of other common abbreviations.

INTRODUCTION

According to the CDC, the number of Americans with a diagnosis of diabetes more than tripled between 1980 and 2012 (from 5.5 million to 21.3 million) (CDC 2014). This number continues to rise, and with it, the number of patients at risk of microvascular and macrovascular complications. Foot problems are common in patients with diabetes. Complications related to foot diseases in patients with diabetes include Charcot arthropathy, foot ulceration, infection, osteomyelitis, and limb amputation. However, the development of a diabetic foot ulcer (DFU) and subsequent infection is preventable. Pharmacists play a vital role by monitoring, educating, and empowering patients. This chapter focuses on the treatment of diabetic foot infections (DFIs), including osteomyelitis, in the primary care setting.

Epidemiology and Impact

Among patients with diabetes, diseases of the feet are more common in men and in individuals older than 60 years. In their lifetime, about 25% of patients with diabetes will have a significant skin and soft tissue infection (SSTI) because of predisposing vascular insufficiency, neuropathy, and impaired immunity. The most common foot infections are DFIs, and these patients have higher recurrence and hospitalization rates (Lipsky 2012). Diabetic foot infections decrease quality of life and increase morbidity, physical and emotional distress, and health care costs. The number of hospital discharges for patients with diabetes and peripheral arterial disease, ulcer/inflammation/infection, and neuropathy doubled from 445,000 in 1988 to 890,000 in 2007 (CDC 2014).

Diabetic foot infections can spread contiguously to deeper tissues, including bone. If the infection progresses, it may eventually be necessary to amputate the limb. The mean hospital charge for one episode of foot or toe osteomyelitis is around $19,000. In addition, in 1988−2009, hospital discharges for nontraumatic lower-extremity amputation in patients with diabetes increased by 24% (CDC 2014).

PATHOGENESIS

Risk Factors for DFUs and Infection

Foot ulcers and infection usually occur after trauma. Several factors predispose a patient with diabetes to foot ulcers and infections. Patients with diabetes often have peripheral sensory and motor neuropathy: diabetic neuropathy increases the risk of foot ulcers by 7-fold (Khanolkar 2008). Patients with diabetes lose the protective sensations for temperature and pain and are often unaware of trauma to their feet. Furthermore, motor neuropathy leads to wasting away of muscle, difficulty walking and standing, loss of reflexes, and foot deformities, among other problems. Therefore, regular foot care is essential to prevent foot ulcers and associated morbidity and mortality in patients with diabetes. A comprehensive yearly foot examination is recommended; patients with a history of ulcers, amputations, foot deformities, peripheral neuropathy, and peripheral arterial disease should have their feet examined at every visit.

Other risk factors for foot ulcers and infection include poor glucose control, which impairs immunologic function, especially action of polymorphonuclear (PMN) leukocytes, humoral immunity, and cell-mediated immunity. In addition, patients with diabetes may have decreased local and systemic inflammatory responses to infection and poor wound healing because of peripheral arterial disease in the affected limb. Peripheral arterial disease is present in 20%−30% of patients with diabetes and in up to 40% of those with DFI; it is also the most important predictor for recovery after DFI (Schaper 2012). A multivariate analysis showed that the risk factors most associated with developing foot infections were wounds that penetrated to the bone (OR 6.7), lasted more than 30 days (OR 4.7), were recurrent (OR 2.4), that had a traumatic etiology (OR 2.4), or that occurred in patients with peripheral vascular disease (OR 1.9) (Lavery 2006). Box 1-1 lists the risk factors for DFIs.

Complications

Breaks in skin expose underlying tissues to colonization by pathogenic organisms including multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA). The resulting infection may begin superficially, but with a delay in treatment and the impaired body defense mechanisms caused by neutrophil dysfunction and vascular insufficiency, it can spread to the contiguous subcutaneous tissues and deeper structures (e.g., bone). Diabetic foot osteomyelitis (DFO) is present in up to 20% of mild-moderate DFIs and 50%−60% of severely infected wounds. Diabetic foot osteomyelitis increases the likelihood of surgical intervention, including amputation.

Patients with DFIs may also present with signs of systemic inflammatory response syndrome, as manifested by at least

Box 1-1. Risk Factors for Diabetic Foot Infections

- Presence of peripheral vascular disease in the affected limb
- Poor glycemic control
- Loss of protective sensation (i.e., neuropathy)
- Traumatic foot wound
- Ulceration > 30 days
- History of recurrent foot ulcers
- Previous lower-extremity amputation
- Improper footwear
- Wounds that penetrated to bone

two of the following: WBC greater than 12×10^3 cells/mm^3 or less than 4×10^3 cells/mm^3 or 10% bands or more; respiratory rate greater than 20 breaths/minute or Paco$_2$ less than 32 mm Hg; temperature greater than 38°C or less than 36°C; and heart rate greater than 90 beats/minute.

ASSESSMENT

Is It Infected?

Not all DFUs are infected. Therefore, DFIs must be diagnosed clinically, rather than only reviewing wound culture results, because microorganisms can colonize all wounds. Local signs and symptoms of infection include swelling, warmth, tenderness, pain, erythema, and purulent secretions. Patients with peripheral neuropathy may be unable to describe pain at the infection site. In addition, patients with limb ischemia secondary to peripheral vascular disease may not have erythema, warmth, or swelling around the infected ulcer. In these patients, it may be appropriate to seek secondary signs of infection, such as abnormal coloration around the wound, a fetid odor from the infected ulcer, friable granulation tissue, and undermining of the wound edges.

Systemic signs and symptoms of infection may be absent in up to 50% of patients. Presence of systemic signs and symptoms suggests severe infection with extensive tissue involvement or a more virulent pathogen. Systemic signs and symptoms include fever, chills, delirium, diaphoresis, anorexia, hemodynamic instability, and metabolic derangements (e.g., acidosis, azotemia, electrolyte abnormalities). Patients may also have leukocytosis and elevated nonspecific inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). These inflammatory markers can be tracked and may help determine when a DFI has resolved, allowing discontinuation of antibiotic therapy.

Classification of Infection

There are several published classification schemes and wound scoring systems; however, none is considered to be a gold standard. Examples of classification schemes are those from the International Working Group on the Diabetic Foot (IWGDF) and the Infectious Diseases Society of America (IDSA). The IWGDF classifies diabetic foot wounds using the acronym PEDIS (perfusion, extent, depth, infection, sensation). The PEDIS grades for DFI are 1–4, with the lowest grade for no symptoms or signs of infection and the highest grade for presence of local and systemic signs and symptoms of infection. The IDSA classifies the infection as uninfected, mild, moderate, or severe. Grading or classification is based on local and systemic manifestations, and extent of infection. Table 1-1 summarizes the IWGDF and IDSA classification systems.

Microbiology

For uninfected wounds, specimen collection for culture is not recommended because it will likely yield only skin flora and microorganisms and lead to unnecessary antimicrobial therapy. For patients who have not been treated with antibiotics in the past 30 days and have a mild DFI, infections are often monomicrobial. The most common causative organisms are aerobic gram-positive bacteria present on the skin surface such as β-hemolytic streptococci (*Streptococcus pyogenes, Streptococcus agalactiae*) or *S. aureus*. In contrast, infections are usually polymicrobial in patients with diabetes who have used antibiotics in the past 30 days and in those with deep, limb-threatening infections or chronic non-healing wounds. Anaerobic bacteria are generally part of polymicrobial infections in wounds with malodorous discharge, limb ischemia, or gangrene. In one study, most patients with moderate to severe DFIs had polymicrobial infections (83.8% of

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Table 1-1. Classification of DFI: PEDIS and IDSA

Clinical Manifestation of Infection	PEDIS Grade	IDSA Infection Severity
No symptoms or signs of infection	1	Uninfected
Local infection (only skin and subcutaneous tissue). If erythema, must be > 0.5 cm to ≤ 2 cm around the ulcer	2	Mild
Local infection with erythema > 2 cm, or infection involving deeper tissues (e.g., abscess, osteomyelitis, septic arthritis, fasciitis) **and** < 2 signs of the systemic inflammatory response syndrome (SIRS)	3	Moderate
Local infection with ≥ 2 signs of SIRS: Temperature > 38°C or < 36°C, HR > 90 beats/min, RR > 20 breaths/min or Paco$_2$ < 32 mm Hg and WBC > 12×10^3 cells/mm^3 or < 4×10^3 cells/mm^3 or ≥ 10% bands	4	Severe

HR = heart rate; RR = respiratory rate.

Information from: Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:132-73.

427 cultures). Cultures yielded 1145 aerobic strains and 462 anaerobic strains, with an average of 2.7 aerobic organisms per culture (range 1–8) and 2.3 anaerobic organisms per culture (range 1–9) (Citron 2007).

In infected wounds, it is crucial to obtain appropriate cultures to guide antibiotic therapy. Deep-tissue specimens obtained after wound cleansing and debridement will yield true pathogens more reliably than specimens from superficial wound swabs, which are often contaminated with normal skin flora and colonizers. Less virulent bacteria such as coagulase-negative staphylococci, Enterococcus sp., and corynebacteria may not be true pathogens (Lipsky 2004). The analysis of WBCs at the site of culture is very important. When reported with a Gram stain, the presence of PMN WBCs in a wound culture is predictive of infection rather than colonization. Anaerobic bacteria will not grow well in cultures taken from open wound cultures; hence, a Gram stain may be the only indication of these organisms. Treatment with antimicrobials before culture will also decrease the growth of bacteria in the laboratory. The Gram stain does not typically have this limitation because it can detect recently dead and dying organisms. Therefore, Gram stain results should be considered when developing a treatment plan.

Risk Factors

Isolation of drug-resistant organisms such as MRSA and Pseudomonas aeruginosa from DFI is on the rise. Understanding a patient's risk factors for these two organisms will help in selecting an optimal empiric regimen for patients who present with DFIs.

Methicillin-Resistant *S. aureus*

Risk factors for MRSA infections (Box 1-2) necessitate its empiric treatment; these include a history of MRSA infection or colonization within the past year, use of antibiotics in the past month, hospitalization in the past year, presence of osteomyelitis, prison incarceration, close contact with a person with a similar infection, purulent drainage, and high local prevalence of MRSA colonization and infection. For example,

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Box 1-2. Risk Factors for MRSA

- History of MRSA infection or colonization within the past year
- Receipt of antibiotics in the past month
- Hospitalization in the past year
- Presence of osteomyelitis
- Prison inmates
- Close contact with a person who has a similar infection
- Purulent drainage
- High local prevalence of MRSA (≥ 50% for mild infections, ≥ 30% for moderate infections)
- Severe diabetic foot infection

MRSA = methicillin-resistant Staphylococcus aureus.

Box 1-3. Risk Factors for *P. aeruginosa*

- Warm climate
- Frequent exposure of the foot to water (soaking feet)
- Treatment failure with antibiotic therapy that has no activity against *P. aeruginosa*
- High local prevalence of *P. aeruginosa* (> 10% of diabetic foot wounds)
- Severe diabetic foot infection

Information from: Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:132-73.

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if at least 50% of all *S. aureus* isolates in the local area are methicillin resistant, empiric activity against MRSA is indicated for mild infection. For moderate DFIs, antibiotics with empiric activity against MRSA are recommended when the local prevalence for MRSA is 30% or more. However, for all severe DFIs, empiric activity against MRSA is recommended (Lipsky 2012; Moran 2006).

P. aeruginosa

Studies of complicated SSTI and DFI show that *P. aeruginosa* is isolated in less than 10% of wounds (in studies primarily from developed northern countries) (Noel 2008; Lipsky 2005). Even though it is a virulent organism, these bacteria are often a nonpathogenic colonizer of the feet, and patients can improve, even with therapy ineffective against *P. aeruginosa*, if proper debridement and wound care are performed. In a study comparing piperacillin/tazobactam with ertapenem in patients with isolates of *P. aeruginosa*, clinical response rates in DFIs were similar in both groups (70% vs. 83.3%, respectively; 95% CI, -18.2 to 48.7), even though ertapenem has no activity against the organism (Lipsky 2005). Risk factors for DFIs caused by *P. aeruginosa* are listed in Box 1-3). For all severe DFIs, empiric activity against *P. aeruginosa* is recommended.

TREATMENT

For clinically uninfected wounds, no antimicrobial therapy is required. Unnecessary use of antibiotics leads to antibiotic resistance, *Clostridium difficile* diarrhea, financial burden, and preventable adverse events. However, all infected wounds should be treated with antimicrobial therapy and appropriate wound care. Empiric antimicrobial therapy for DFIs should be based on the severity of the infection and the likely causative pathogen. Regardless of the antimicrobial, the best predictor of successful treatment is proper wound care, including drainage.

For patients with mild to moderate DFIs and no history of recent antibiotic use (i.e., in the past 30 days), empiric antibiotic therapy should target gram-positive cocci present on the skin, *S. pyogenes* (group A *Streptococcus*) and methicillin-sensitive *S. aureus* (MSSA). For mild to moderate DFIs with

an abscess or purulence, or if the patient has risk factors for MRSA (see Box 1-2), antimicrobial therapy targeting MRSA and group A *Streptococcus* should be used. For patients with mild to moderate DFIs and antibiotic use within the past 30 days, empiric antimicrobial therapy should also target gram-negative bacilli. Empiric therapy directed at *P. aeruginosa* is usually unnecessary except for patients with risk factors for this organism (see Box 1-3).

For severe DFIs, broad-spectrum antimicrobial therapy targeting gram-positive cocci, gram-negative bacilli, and obligate anaerobes is recommended, including activity against MRSA and *P. aeruginosa.* Antimicrobial therapy should then be tailored to the results of an appropriately obtained Gram stain and culture plus the patient's clinical response. For mild and many moderate DFIs, oral antibiotics can be used in patients for whom an antimicrobial with the appropriate spectrum is available. For some moderate DFIs and for severe DFIs that require parenteral therapy initially, oral therapy can be used sequentially as a step-down once the patient is stable and infection is not progressing. Table 1-2 lists suggested empiric antimicrobial regimens for mild, moderate, and severe DFIs.

Empirically, every effort must be made to preserve the use of broader-spectrum and costlier antimicrobials. Newer, expensive anti-MRSA agents (e.g., ceftaroline, daptomycin, linezolid, tedizolid, dalbavancin, oritavancin, telavancin, tigecycline) provide no additional benefit in efficacy outcomes over vancomycin, because studies of skin and skin structure infection have not proved them superior to vancomycin. Although these newer agents can be used because of vancomycin intolerance or failure, vancomycin is still preferred as the first-line intravenous anti-MRSA agent. Antipseudomonal agents (piperacillin/tazobactam, ceftazidime, cefepime, imipenem, doripenem, meropenem) should only be used when *P. aeruginosa* is suspected and the infection is life or limb threatening. Even then, immediate de-escalation should occur once the results of cultures and susceptibility testing are available.

Carbapenems are the drugs of choice for treating infections caused by Enterobacteriaceae that produce extended-spectrum β-lactamases. These agents may be initiated empirically in patients with a history of infections caused by extended-spectrum β-lactamase−producing Enterobacteriaceae. Consulting local antibiograms may be important because an increasing number of Enterobacteriaceae are resistant to amoxicillin/clavulanate, ampicillin/sulbactam, ciprofloxacin, levofloxacin, and trimethoprim/sulfamethoxazole.

Although many antimicrobials are used clinically to treat soft tissue infections, only three have FDA-approved labeling for DFIs: piperacillin/tazobactam, linezolid, and ertapenem. In 2010, the FDA issued guidance for developing systemic drugs to treat acute bacterial skin and skin structure infections. Infections needing more complex treatment regimens, including DFIs, were excluded. Hence, few new data have been published in this area.

Ceftaroline is an advanced-generation cephalosporin with activity against MRSA as well as other gram-positive skin pathogens. It was approved for treatment of skin and skin structure infections in 2011, although not indicated for diabetic foot infections. Ceftaroline has activity against some gram-negative organism but is not effective against most anaerobes.

Table 1-2. DFI Microbiology and Recommended Empiric Antibiotic Therapy According to Severity

Severity	Pathogens[a]	Drugs
Mild-moderate • Outpatient management • Treated with oral agents	*Streptococcus* sp., and MSSA MRSA (for risk factors, see Box 1-2)	• Dicloxacillin, cephalexin, clindamycin, or amoxicillin/clavulanate • Clindamycin, doxycycline, minocycline, trimethoprim/sulfamethoxazole, or linezolid
Moderate • Hospitalization warranted • May be treated initially with parenteral agents	MRSA, gram-negative bacilli, anaerobes	• Vancomycin + ampicillin/sulbactam, moxifloxacin, cefoxitin, or cefotetan • Vancomycin + metronidazole + ceftriaxone, ciprofloxacin, or levofloxacin
Severe • ICU admission • Life or limb threatening	MRSA, gram-negative bacilli including *P. aeruginosa*, anaerobes	• Vancomycin + piperacillin/tazobactam, imipenem/cilastatin, meropenem, or doripenem • Vancomycin + metronidazole + ceftazidime, cefepime, ciprofloxacin, or levofloxacin

[a]Treat for MRSA in patients with risk factors as described in Box 1-2; treat for *P. aeruginosa* in patients with risk factors as described in Box 1-3.

Information from: Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:132-73.

In 2014, three new antimicrobials were approved for the treatment of skin and skin structure infections: tedizolid, oritavancin, and dalbavancin. However, data are limited on the use of these agents in DFIs and osteomyelitis. Tedizolid is an oxazolidinone, similar to linezolid, but can be dosed once-daily instead of twice. It might be less likely to interact with serotonergic agents, although human clinical data on this are lacking. Tedizolid also may cause less thrombocytopenia than linezolid, but trials with the drug for acute bacterial skin and skin structure infections focused on a short treatment course (6 vs. 10 days), and this adverse effect is more likely to occur after 2–3 weeks of therapy with linezolid.

Oritavancin and dalbavancin are both long-acting lipoglycopeptides with mechanisms of action similar to those of both vancomycin and telavancin. The half-lives of these drugs are over 240 hours with very little removal by dialysis, should an adverse event occur. Of patients receiving oritavancin in clinical trials, 14% had diabetes. The prescribing information carries a warning not to use the drug in patients with suspected osteomyelitis; this is because osteomyelitis developed more often in patients treated with oritavancin than in those treated with vancomycin. At the end of the SOLO II trial, five patients in the oritavancin group had osteomyelitis versus none in the vancomycin arm. Osteomyelitis occurred within 1–9 days of oritavancin administration, which suggests that

osteomyelitis existed at the time of study entry (Corey 2015). Oritavancin can artificially prolong coagulation tests, including activated clotting time, prothrombin time, and INR. This can be a concern in the ambulatory patient population taking warfarin, which may not be monitored closely. The average wholesale price of the lipoglycopeptides is around $3000 per initial dose. Favorable bone concentrations of dalbavancin above the MIC for common gram-positive pathogens that cause bone and joint infections have been observed in rabbits (Solon 2007). In addition, results were recently replicated in human volunteers undergoing knee and hip arthroplasties (Dunne 2015).

A coordinated and multidisciplinary team approach is recommended for managing DFIs. This team should include infectious diseases physicians for treatment recommendations and management of appropriate antibiotic therapy, microbiologists for accurate identification of organisms, a general surgeon for appropriate debridement and drainage, vascular surgeons if the limb is ischemic, nurses, podiatrists, wound care specialists, and pharmacists for medication supervision and counseling, as well as diabetes education and management.

Topical Therapy

Several topical antibiotic preparations are available, including some OTC products, which may be suitable for use in

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Patient Care Scenario

A 72-year-old man (weight 91 kg) presents with a 3-day history of right foot swelling, erythema, and pain, with a yellow foul-smelling purulent discharge from a foot ulcer. The erythema is 3 cm around the ulcer. His medical history is significant for type 2 diabetes (A1C 1 week ago was 9.5%), hypertension, peripheral neuropathy, peripheral vascular disease, and a 15-month history of a diabetic right foot ulcer. The patient has no antibiotic allergies. The patient has no systemic signs of infection, and the physician asks you to develop an antimicrobial regimen for this patient.

- What are the patient's risk factors for DFI?
- How would you classify this patient's infection?
- What would be this patient's empiric antimicrobial regimen?

ANSWER

This patient has several risk factors for DFI, including a chronic foot ulcer (greater than 30 days), uncontrolled diabetes (A1C 9.5%), peripheral neuropathy, and peripheral vascular disease. According to the IWGDF classification, he would be assigned a PEDIS grade 3, and according to the IDSA classification, he has a moderate DFI. This is because the patient has no systemic manifestations, but local signs and symptoms of infection for the patient include swelling, erythema, pain, and yellow foul-smelling purulent discharge from ulcer. In addition, the erythema around the ulcer is 3 cm.

The patient should have any underlying abscess drained and cultured to identify the organism(s) and

susceptibilities. For moderate infection, oral or intravenous antimicrobials can be used (see Table 1-2). Because the patient has purulent discharge, MRSA should be targeted with empiric therapy. Other organisms that should be covered include group A streptococci, gram-negative bacilli (e.g., Enterobacteriaceae but not P. aeruginosa), and anaerobes. All antibiotic options for the treatment of moderate DFI listed in Table 1-2 are reasonable: vancomycin plus ampicillin/sulbactam, moxifloxacin, cefoxitin, or cefotetan; or vancomycin plus metronidazole plus ceftriaxone, ciprofloxacin, or levofloxacin. Local antibiograms should be consulted because of the increasing resistance to fluoroquinolones and ampicillin/sulbactam seen among those with Enterobacteriaceae.

1. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:132-73.
2. Bader MS. Diabetic foot infection. Am Fam Physician 2008;78:71-9.

treating mild DFI. Examples are mupirocin, retapamulin, triple antibiotic cream/ointment (which contains bacitracin, neomycin, and polymyxin B), and double antibiotic cream/ointment (which contains bacitracin and polymyxin B). Other topical antibiotic preparations such as topical clindamycin, erythromycin, benzoyl peroxide, sulfacetamide, and dapsone are limited to the treatment of Propionibacterium acnes, which is not a likely pathogen of the feet. Topical antifungal and antiviral preparations are also available, but they have a negligible role in DFIs.

Topical treatment avoids systemic adverse events, provides drug therapy at the site of action, and allows the use of agents not available for systemic therapy or too toxic for routine use in DFI (e.g., polymyxin B). However, topical therapy should only be used for mild, superficial, and small DFIs. Limited and conflicting data exist for using topical antimicrobial therapy for mild DFIs. In two consecutive double-blind, controlled trials (study 303 and 304), patients with mild DFIs were randomized to receive either topical pexiganan or oral ofloxacin. Topical pexiganan is a broad-spectrum peptide antimicrobial with activity against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria, including *S. aureus* and *P. aeruginosa.* The primary outcome of these two trials was clinical cure or improvement of the infection. For study 303, the pexiganan arm failed to show equivalence in clinical cure or improvement to the ofloxacin arm (85% vs. 91.1%; 95% CI, -11.74 to -0.33). Study 304, however, showed the pexiganan arm to be equivalent to the ofloxacin arm in clinical cure or improvement (89.5% for both treatment arms; 95% CI, -6.51 to 6.51) (Lipsky 2008).

Topical therapy does not attain deep tissue penetration or systemic therapeutic concentrations; as a result, topical antimicrobial therapy for DFIs is only useful when a superficial wound is first developing infection. Because of the lack of robust evidence of efficacy and concern for adverse events, high cost, and drug resistance, use of topical antimicrobials, including iodine and silver-based dressings, is not routinely recommended to decrease the bioburden of a diabetic foot wound or for the treatment of uninfected diabetic foot wounds.

Oral Therapy

For mild and many moderate DFIs, oral antibiotics can be used. For some moderate DFIs and severe DFIs that initially require parenteral therapy, oral therapy can be used as a step-down once the patient is stable and infection is not progressing. Oral antibiotics with high bioavailability and equivalent intravenous-to-oral conversions are desirable for deep-seated DFIs and DFO. Although some oral β-lactams such as amoxicillin and cephalexin have fairly high bioavailability, they lack equivalent intravenous-to-oral conversions. For example, in a patient with normal renal function, cefazolin may be dosed at 1–2 g intravenously every 8 hours; however, oral cephalexin is usually dosed at 500 mg every 6 hours

because of GI intolerance at higher doses. This is important because of the high rate of peripheral vascular disease in patients with diabetes and the limited amount of drug that can reach the infection site. Other antibiotics with excellent bioavailability that have equivalent intravenous-to-oral conversions (1:1, unless noted) include levofloxacin, moxifloxacin, ciprofloxacin (0.8:1), trimethoprim/sulfamethoxazole, linezolid, tedizolid, doxycycline, minocycline, and metronidazole. Although 90% of oral clindamycin is absorbed, doses greater than 600 mg orally every 8 hours are generally not well tolerated because they lead to GI adverse effects.

For patients with risk factors for MRSA, linezolid has the most evidence and has been proved at least as effective as vancomycin. Linezolid has very high tissue penetration, even with the oral formulation. Generic linezolid is now available commercially. However, it is still more expensive than older drugs, and patient assistance programs will no longer be available.

Historically, trimethoprim/sulfamethoxazole has been used as an alternative for minor infections, but it is considered less effective than vancomycin for serious infections. Trimethoprim/sulfamethoxazole also has questionable activity against group A streptococci, as evidenced by its higher failure rates for streptococcal pharyngitis than β-lactams. This has led some experts to recommend combination therapy with trimethoprim/sulfamethoxazole plus a β-lactam for treatment of skin infections when the etiology is unknown.

Doxycycline is another orally available option for the treatment of minor MRSA skin infections. It has concerns similar to trimethoprim/sulfamethoxazole regarding efficacy against β-hemolytic streptococci.

Clindamycin has better streptococcal activity, but resistance is high for hospital-acquired MRSA in some areas. This is a concern in patients with diabetes who are often exposed to the health care system. In a recent study of treatment for community-acquired skin infections with a high MRSA rate (e.g., cellulitis, abscesses), there was no difference between clindamycin and trimethoprim/sulfamethoxazole; however, patients with diabetes were excluded (Miller 2015).

Fluoroquinolones are not recommended as single agents for treatment of infections caused by *S. aureus* because of the potential for resistance to develop during treatment. The FDA recently issued a warning against their use for minor infections because of concern over serious adverse events that can occur with this class (FDA 2016).

Intravenous Therapy

Although many patients with moderate and even severe DFIs may be de-escalated from intravenous to oral antibiotics, others (especially those with DFO) will require intravenous antibiotics for the entire therapy. Most of these patients will be stable enough to receive this treatment outside the hospital; this is known as outpatient parenteral antimicrobial therapy (OPAT). The IDSA has published guidelines on the

proper treatment of OPAT patients (Tice 2004). No single drug or combination of agents appears to be superior to others for OPAT; treatment should be tailored to culture results and the most probable pathogens.

Tigecycline, which did not meet the noninferiority criteria compared with ertapenem in patients with DFIs, including some with osteomyelitis, is not generally recommended. In this phase III, randomized, double-blind, multicenter trial, the safety and efficacy of tigecycline 150 mg intravenously daily and ertapenem 1 g intravenously daily were compared with or without vancomycin in patients with DFIs with and without osteomyelitis. In the modified intention-to-treat analysis, 71.4% of the patients who received tigecycline had clinical cure compared with 77.9% in the ertapenem with or without vancomycin arm (95% CI for difference, -12.3 to -1.1). The noninferiority of tigecycline to ertapenem with or without vancomycin for clinical cure was determined using the lower limit of a two-sided 95% CI. If the lower limit of the two-sided 95% CI is not less than -10%, noninferiority is concluded. As a result, in this study, tigecycline did not meet the criteria for noninferiority and was therefore not approved for this indication. Nausea and vomiting occurred significantly more often in the tigecycline arm than in the ertapenem arm (39.8% vs. 8.4% and 24.7% vs. 4.7%, respectively), resulting in significantly higher discontinuation rates in the tigecycline arm (Lauf 2014).

Studies with trimethoprim/sulfamethoxazole have shown patterns of hypoglycemia and increased ED visits when coadministered with sulfonylurea drugs, making this combination undesirable (Tan 2015; Parekh 2014). Table 1-3 lists the common antibiotics used in DFIs, together with their spectrum of activity, dosing regimens, and adverse reactions.

Definitive Antimicrobial Therapy

Initial therapy for DFIs is empiric and guided by the clinical presentation and the patient's risk factors for multidrug-resistant organisms such as MRSA, Enterobacteriaceae that produce extended-spectrum β-lactamase, and P. aeruginosa. Pathogen identification and susceptibilities may take 3–5 days. Once these results are known, the antibiotic spectrum should be narrowed to specifically target the isolated pathogens. This is critical because it can reduce cost, reduce toxicity, minimize collateral damage (e.g., C. difficile diarrhea), and prevent the emergence of drug-resistant organisms. This is especially important for the carbapenem and advanced-generation cephalosporin classes of antibiotics because their broad-spectrum activity can easily predispose patients to C. difficile infection. There is also increasing resistance to carbapenems in the United States and throughout the world.

Duration of Antimicrobial Therapy for DFIs

Duration of antimicrobial therapy should be based on severity of infection, bone involvement, and clinical response. There is no good evidence to continue antibiotic therapy until the wound is fully healed; this will be an extended period for many patients because of poor would healing properties. Table 1-4 lists the recommended duration of antibiotic therapy for DFIs (without involvement of bone).

Wound Care

Patients with diabetic foot wounds should receive appropriate wound care to ensure optimal healing. Antibiotic therapy for infected wounds may be insufficient unless combined with appropriate wound care. To ensure proper healing, the wound must be well vascularized, free of debris and necrotic tissue, free of infection, and moist. Standard wound care includes debridement, redistribution of pressure off the wound, and moist wound dressings.

Debridement

Debridement of the wound removes debris, colonizing bacteria, necrotic and nonviable tissue, and any surrounding callus. In addition, it aids in granulation tissue formation, angiogenesis, and promotion of the growth of new tissue, hence enabling wound healing. Sharp debridement with a scalpel, scissors, or tissue nippers is preferred. Other methods of debridement include biological debridement with maggots and enzymatic debridement (e.g., with collagenase [Santyl]), which is FDA approved for debriding chronic dermal ulcers and severely burned areas.

Off-Loading Pressure

Redistributing pressure off the wound is an important component of appropriate wound care. The total contact cast device redistributes pressure to the entire weight-bearing surface to accelerate the healing of an ulcer.

Wound Dressings

Because diabetic foot wounds are heterogeneous, no single dressing is perfect; rather, a clinician should evaluate individual wounds and choose the best dressing on a case-by-case basis. Creating a moist wound environment helps promote granulation, angiogenesis, and wound healing. Types of dressings include continuously moistened saline gauze for dry or necrotic wounds, hydrogels for dry and necrotic wounds to facilitate autolysis, occlusive and semi-occlusive films for making dry wounds moist, alginates for drying exudative wounds, hydrocolloids for absorbing exudates and to facilitate autolysis, and foams for exudative wounds (Lipsky 2012).

Adjunctive Treatments

Adjunctive treatments such as hyperbaric oxygen therapy (HBOT), platelet-derived growth factors, granulocyte colony-stimulating factor (G-CSF), and bioengineered skin equivalents lack robust evidence to support their routine use in DFI treatment. These treatment modalities are expensive and may not be feasible in a resource-limited setting.

Table 1-3. Common Antibiotics Used for DFIs

Agent	Antibacterial Activity	Dosing Regimen[a]	Common Adverse Effects
Penicillins			
Amoxicillin/ clavulanate	Gram-negative bacilli[b]: *Escherichia coli, Proteus* sp., *Klebsiella* sp. Gram-positive cocci: MSSA, *Enterococcus faecalis*, group A streptococci, viridans streptococci Anaerobes: *Bacteroides* sp., *Peptostreptococcus* sp., *Finegoldia magna, Propionibacterium* sp.	875 mg of amoxicillin PO q12hr or 500 mg of amoxicillin PO q8hr 2 g ER PO q12hr may be preferred for bone infections	GI upset, diarrhea
Ampicillin/ sulbactam	Gram-negative bacilli[b]: *E. coli, Proteus* sp., *Klebsiella* sp., *Acinetobacter baumannii* Gram-positive cocci: MSSA, *Enterococcus faecalis*, group A streptococci, viridans streptococci Anaerobes: *Bacteroides* sp., *Peptostreptococcus* sp., *F. magna, Propionibacterium* sp.	3 g IV q6hr	GI upset, diarrhea, rash
Dicloxacillin	Gram-positive cocci: MSSA, group A streptococci	500 mg PO q6hr	Nausea
Nafcillin	Same as dicloxacillin	1–2 g IV q4–6hr	Rash, diarrhea, nausea
Oxacillin	Same as dicloxacillin	1–2 g IV q4–6hr	Rash, diarrhea, nausea
Piperacillin/ tazobactam	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp., *P. aeruginosa, A. baumannii* Gram-positive cocci: MSSA, group A streptococci, *viridans streptococci, E. faecalis* Anaerobes: *Bacteroides* sp., *Peptostreptococcus* sp., *F. magna, Propionibacterium* sp.	3.375 g IV q6hr or 4.5 g q8hr 4.5 g IV q6hr for osteomyelitis or *Pseudomonas* infection	Rash, diarrhea
Cephalosporins			
Cefazolin	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp. Gram-positive cocci: MSSA, group A streptococci	2 g IV q8hr	None significant
Cefepime	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp., *P. aeruginosa* Gram-positive cocci: MSSA, group A streptococci, viridans streptococci	1–2 g IV q8–12hr	Neurologic, myoclonus, *C. difficile* diarrhea
Cefotetan	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp. Gram-positive cocci: MSSA, group A streptococci Anaerobes: *Bacteroides* sp.,[b] *Peptostreptococcus* sp., *F. magna, Propionibacterium* sp.	1–2 g IV q8–12hr	*C. difficile* diarrhea, prolonged prothrombin time
Cefoxitin	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp. Gram-positive cocci: MSSA, group A *Streptococcus* Anaerobes: *Bacteroides* sp.,[b] *Peptostreptococcus* sp., *F. magna, Propionibacterium* sp.	1–2 g IV q6–8hr	*C. difficile* diarrhea

(continued)

Table 1-3. (*Continued*)

Ceftaroline	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp. Gram-positive cocci: MSSA, MRSA, group A streptococci, viridans streptococci	600 mg IV q12hr	*C. difficile* diarrhea
Ceftazidime	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp., *P. aeruginosa*	1−2 g IV q8hr	*C. difficile* diarrhea
Ceftriaxone	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp. Gram-positive cocci: MSSA, group A streptococci, viridans streptococci	1−2 g IV q24hr	*C. difficile* diarrhea
Cephalexin	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp. Gram-positive cocci: MSSA, group A *Streptococcus*	500 mg PO q6hr	None significant
Carbapenems			
Doripenem	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp., *P. aeruginosa, A. baumannii* Gram-positive cocci: MSSA, group A streptococci, viridans streptococci Anaerobes: *Bacteroides* sp., *Peptostreptococcus* sp., *F. magna, Propionibacterium* sp.	500 mg IV q8hr	*C. difficile* diarrhea
Ertapenem	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp. Gram-positive cocci: MSSA, group A streptococci, viridans streptococci Anaerobes: *Bacteroides* sp., *Peptostreptococcus* sp., *F. magna, Propionibacterium* sp.	1 g IV q24hr	*C. difficile* diarrhea
Imipenem/ Cilastatin	Same as doripenem	500 mg IV q6hr	*C. difficile* diarrhea
Meropenem	Same as doripenem	1 g IV q8hr	*C. difficile* diarrhea
Monobactams			
Aztreonam	Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp., *P. aeruginosa*	1−2 g IV q8hr	None significant
Lincosamides			
Clindamycin	Gram-positive cocci: MSSA, MRSA, group A streptococci, viridans streptococci Anaerobes: *Bacteroides* sp.,[b] *Peptostreptococcus* sp., *F. magna, Propionibacterium* sp.	Oral: 300−450 mg q6hr, 600 mg q8hr IV: 600−900 mg q8hr	*C. difficile* diarrhea, GI upset
Lipopeptides			
Daptomycin	Gram-positive cocci: MSSA, MRSA, *Enterococcus* sp., group A streptococci, viridans streptococci	4 mg/kg IV q24hr for skin and soft tissue infections, 6 mg/kg IV q24h for bacteremia or osteomyelitis, 8−10 mg/kg IV q24hr for severe MRSA infection refractory to vancomycin	Elevated creatinine phosphokinase, eosinophilic pneumonia

Table 1-3. (*Continued*)

Tetracyclines

Doxycycline	Gram-positive cocci: MSSA, MRSA	100 mg IV/PO q12hr	GI upset, photosensitivity
Minocycline	Same as doxycycline	100 mg IV/PO q12hr	GI upset, photosensitivity, dizziness

Oxazolidinones

Linezolid	Gram-positive cocci: MSSA, MRSA, *Enterococcus* sp., group A streptococci, viridans streptococci	600 mg IV/PO q12hr	Myelosuppression, neuropathy, serotonin syndrome
Tedizolid	Gram-positive cocci: MSSA, MRSA, Enterococcus sp., group A streptococci, viridans streptococci	200 mg IV/PO q24hr	Myelosuppression, neuropathy, serotonin syndrome possible

Glycopeptides

Vancomycin	Gram-positive cocci: MSSA, MRSA, *Enterococcus* sp., group A streptococci, viridans streptococci	15 mg/kg IV q12hr, goal trough concentration 10–20 mcg/mL	Nephrotoxicity, red man syndrome

Lipoglycopeptide

Dalbavancin	Gram-positive cocci: MSSA, MRSA, *Enterococcus* sp., streptococci	*Single-dose regimen*: 1500 mg *Two-dose regimen*: 1000 mg IV on day 1, followed by 500 mg on day 8	Infusion reactions
Oritavancin	Gram-positive cocci: MSSA, MRSA, *Enterococcus* sp., streptococci	1200 mg IV single dose	Infusion reactions
Telavancin	Gram-positive cocci: MSSA, MRSA, *Enterococcus* sp., streptococci	10 mg/kg IV daily	Infusion reactions, QT prolongation, nephrotoxicity, foamy urine, dysgeusia

Fluoroquinolones

Ciprofloxacin	Gram-negative bacilli[b]: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp., *P. aeruginosa*	IV: 400 mg IV q8–12hr PO: 500–750 mg PO q12hr	Tendinitis, tendon rupture, *C. difficile* diarrhea, QT prolongation, peripheral neuropathy
Levofloxacin	Gram-negative bacilli[b]: *E. coli, Proteus* sp., *Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp., *P. aeruginosa* (with 750mg dose), Gram-positive cocci: streptococci	500–750 mg IV/PO q24hr	Tendinitis, tendon rupture, *C. difficile* diarrhea, QT prolongation, photosensitivity, peripheral neuropathy, CNS effects (with high doses)
Moxifloxacin	Gram-positive cocci: streptococci Gram-negative bacilli: *E. coli, Proteus* sp., *Klebsiella* sp. Anaerobes: *Bacteroides* sp., *Peptostreptococcus* sp.	400 mg IV/PO q24hr	Tendinitis, tendon rupture, *C. difficile* diarrhea, QTc prolongation, photosensitivity, peripheral neuropathy, CNS effects

Miscellaneous

Metronidazole	Anaerobes: *Bacteroides* sp., *Peptostreptococcus* sp.	500 mg IV/PO q8hr	Metallic taste, nausea, neuropathy

(continued)

Table 1-3. (Continued)

Tigecycline	Gram-negative bacilli: *E. coli, Klebsiella* sp., *Serratia* sp., *Enterobacter* sp., *Citrobacter* sp. Gram-positive cocci: MSSA, MRSA, *Enterococcus* sp., group A streptococci, viridans streptococci Anaerobes: *Bacteroides* sp., *Peptostreptococcus* sp., *F. magna, Propionibacterium* sp.	100 mg IV × 1 load, followed by 50 mg IV q12hr	Nausea, vomiting
Trimethoprim/ sulfamethoxazole	Gram-negative bacilli[b]: *E. coli, Proteus* sp., *Klebsiella* sp. Gram-positive cocci: MSSA, MRSA	PO: 1 double-strength tablet q12hr or 20 mL (160 mg of TMP) q12hr IVc: 3.5−4.0 mg TMP/kg/ dose IV q8−12hr	Rash, hyperkalemia

[a]Dosages based on normal renal and hepatic function.

[b]Increasing resistance, consult local antibiograms.

[c]Limited stability of parenteral admixture at room temperature; 5 mL TMP/125 mL D5W is stable for 6 hours.

ER = extended release; IV = intravenously; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *S. aureus*; PO = by mouth; q = every; TMP = trimethoprim.

Table 1-4. Antibiotic Therapy Duration for DFIs

Severity	Duration
Mild	1−2 wk; 4 wk if slow to resolve
Moderate	1−3 wk
Severe	2−4 wk

DFI = diabetic foot infection.

Information from: Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:132-73.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy has been used as an adjunct to wound care to promote healing. It is designed to increase oxygen delivery to ischemic tissue, hence promoting wound healing and fighting infection. However, data for the use of HBOT in healing diabetic foot wounds are controversial. A longitudinal observational cohort study compared the effectiveness of HBOT with that of other conventional therapies administered in a wound care network for the treatment of a DFU and prevention of lower-extremity amputation. The authors studied 6259 patients with diabetes. Patients receiving HBOT were less likely to have healing of their foot ulcer (HR 0.68; 95% CI, 0.63−0.73) and more likely to have an amputation (HR 2.37; 95% CI, 1.84−3.04) (Margolis 2013).

A prospective, double-blind, randomized controlled clinical trial assessed the efficacy of HBOT in reducing the need for major amputation and promoting wound healing in patients with diabetes and chronic DFUs. Of the 103 patients available for evaluation, the criteria for major amputation were met in 24% of patients (13 of 54) in the placebo group and 22% of patients (11 of 49) in the HBOT group (p=0.846). Healing of the wound was not significantly different between the two groups (20% in the HBOT group and 22% in the placebo group; p=0.823) (Fedorko 2016). Therefore, the use of HBOT cannot be routinely recommended for the healing of DFUs and DFIs.

Platelet-Derived Growth Factors

Becaplermin is a platelet-derived growth factor gel preparation that has FDA-approved labeling for the treatment of lower-extremity diabetic neuropathic ulcers that extend into the subcutaneous tissue or beyond and have an adequate blood supply. This agent improves wound healing by enhancing the formation of new granulation tissue, inducing fibroblast proliferation and differentiation, and promoting angiogenesis. Becaplermin has a boxed warning because in a postmarketing retrospective cohort study, patients treated with three or more tubes of becaplermin had an increased rate of mortality secondary to malignancy (3.9 vs. 0.9 per 1000 person-years) compared with controls. Efficacy of becaplermin in wound healing from clinical trials has not translated into clinical practice (Wu 2007). Routine use of becaplermin for DFUs cannot be recommended because its efficacy has not consistently been demonstrated and because of its high cost (average wholesale price of a 15-g tube of becaplermin is about $1100).

Granulocyte Colony-Stimulating Factor

The few studies available of G-CSF (e.g., filgrastim, peg-filgrastim) do not support the routine use of this therapy for DFIs, although there may be some benefit. Adding G-CSF did

Patient Care Scenario

A 72-year-old man (weight 91 kg) has had a diabetic foot ulcer for 15 months. He presents with a 3-day history of right foot swelling, erythema, and pain, with a yellow foul-smelling purulent discharge from his ulcer. The erythema is 3 cm around the ulcer. His medical history is also significant for type 2 diabetes (A1C 1 week ago was 9.5%), hypertension, peripheral neuropathy, and peripheral vascular disease. The patient has no known drug allergies and no systemic signs of infection. The physician asks you to develop an antimicrobial regimen for him.

Appropriate wound care is given, cultures are obtained, and the patient is initiated on vancomycin intravenously, ceftriaxone intravenously, and metronidazole intravenously. The patient does not have osteomyelitis. After 5 days of therapy, cultures are finalized. The patient has significant improvement because there is no drainage, and the pain, erythema, and swelling are diminished. The physician wants to send the patient home and asks you for antibiotic recommendations. What antibiotic, route, and duration would you recommend for this patient?

MSSA

Drug	Susceptibilities
Penicillin	R
Amoxicillin/clavulanate	S
Oxacillin	S
Clindamycin	R
Linezolid	S
Vancomycin	S
Doxycycline	S
Trimethoprim/sulfamethoxazole	S

Proteus mirabilis

Drug	Susceptibilities
Ampicillin	R
Amoxicillin/clavulanate	S
Levofloxacin	R
Trimethoprim/sulfamethoxazole	R
Cefoxitin	S
Ceftriaxone	S

ANSWER

This patient has had significant improvement after 5 days of intravenous therapy. According to the culture and sensitivities, it would be acceptable to de-escalate antibiotics to amoxicillin/clavulanate monotherapy. Amoxicillin/clavulanate will have activity against the patient's MSSA. Oral therapy is acceptable because the patient does not have osteomyelitis and has had significant improvement after intravenous therapy. According to Table 1-5, 1–3 weeks of antibiotics are recommended for moderate DFIs. Because the duration of antibiotic therapy depends on clinical response, 7–10 days of antibiotics (5 additional days of oral amoxicillin/clavulanate) would be sufficient for this patient.

1. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:132-73
2. Bader MS. Diabetic foot infection. Am Fam Physician 2008;78:71-9.

not significantly affect the resolution of infection or wound healing but was associated with a significant reduction in lower-extremity amputation and length of hospital stay. In one study, 40 patients were randomized to receive conventional treatment (antibiotic therapy plus local treatment) or conventional treatment plus G-CSF. The primary outcome was clinical cure, improvement, failure, and need for amputation. There were no significant differences between the two groups concerning the number of patients either cured or improved or the number of patients with therapeutic failure. However, the cumulative number of amputations observed after 9 weeks of treatment appeared to be lower in the

conventional treatment plus G-CSF arm. Only three patients (15%) in this group required amputation compared with nine patients (45%) in the conventional treatment group (p=0.038) (de Lalla 2001). The IDSA guidelines do not recommend the routine use of G-CSF for the treatment of DFIs because robust evidence is lacking.

Bioengineered Skin Equivalents

Human skin grafts and bioengineered skin substitutes (e.g., Dermagraft, Apligraf, TheraSkin) have been studied in patients with noninfected, nonischemic chronic DFUs. In a systemic review and meta-analysis, five trials using skin grafts or substitutes for DFU treatment met the inclusion criteria and were included. The prespecified primary end point was complete healing rate at the end of the trial. This meta-analysis favored the intervention group (bioengineered skin equivalents) compared with standard care (OR 1.46; 95% CI, 1.21–1.76) (Blozik 2008). Because of limited high-level evidence, the IDSA guidelines for DFIs do not recommend routine use of bioengineered skin equivalents for DFUs.

DIABETIC FOOT OSTEOMYELITIS

Diabetic foot osteomyelitis is present in up to 20% of mild to moderate infections and in 50%–60% of severely infected wounds. Diabetic foot osteomyelitis occurs because of the contiguous spread of infection from a DFU with or without direct trauma to the bone. The presence of DFO increases the likelihood of surgical interventions, including amputations.

Diagnosis

The gold standard for diagnosing osteomyelitis combines isolation of bacteria from a reliable sample of bone with histologic findings of osteonecrosis and inflammation. If obtaining a bone sample is not feasible, the diagnosis of osteomyelitis is made using a combination of clinical, radiographic, and laboratory findings. Diabetic foot osteomyelitis is suggested in patients who have large (greater than 2 cm) or deep (greater than 3 mm) foot ulcers, in patients when the bone is visible or palpable on a probe-to-bone (PTB) test, and in patients who have good blood supply to the affected foot and whose ulcer does not heal despite at least 6 weeks of appropriate wound care and off-loading (Gemechu 2013; Lipsky 2012).

Magnetic resonance imaging can aid in the diagnosis of DFO. It has high sensitivity and specificity and is the most accurate imaging study for defining bone infection. In a patient with a DFU, the PTB test can be helpful in diagnosing DFO. The PTB test involves probing for bone with a sterile blunt wooden or metal tool. For an infected diabetic foot wound, a positive PTB test has a high positive predictive value for osteomyelitis. However, a negative PTB test does not exclude osteomyelitis. One study assessed the relationship between detection of bone using the PTB test and the presence or absence of DFO that was defined clinically and/or histopathologically. Of the 76 infected DFUs studied, 66%

(n=50) had osteomyelitis. Of these 50 ulcers, 33 (66%) had a positive PTB test. Four of the 26 ulcers (15%) that did not have osteomyelitis had a positive PTB test. Therefore, the PTB test had a sensitivity of 66% for osteomyelitis, specificity of 85%, positive predictive value of 89%, and negative predictive value of 56% (Grayson 1995).

Microbiology

S. aureus is the most common pathogen isolated in DFO. Despite being considered a contaminant in SSTIs, the second most common organism involved in DFO is *Staphylococcus epidermidis*. The most likely gram-negative bacilli to be cultured include *E. coli, Klebsiella pneumoniae, Proteus* sp., and *P. aeruginosa*. Isolation of obligate anaerobes in DFO is low; the most common are *Peptostreptococcus* sp., *F. magna*, and *Peptococcus* sp. In a retrospective chart review of 80 patients with DFO who underwent a bone biopsy, 129 bacterial isolates were cultured, 54% of which were polymicrobial. The most common organism was *S. aureus* (33% of all isolates). Gram-negative bacilli and anaerobes made up 20% and 4%, respectively, of the cultured microorganisms (Lesens 2011).

Treatment

The clinical evidence base regarding treatment regimens for DFO is poor. Similar to DFIs, no data support the superiority of one drug or combination of drugs, route, or therapy duration. In a retrospective study of patients with DFO, the rate of resolution of bone infection without surgery was significantly higher when antibiotic therapy was directed by bone culture compared with empiric therapy (56.3% vs. 22.2%; p=0.04) (Senneville 2008).

Antibiotic therapy selected for the treatment of DFO should have good bone penetration. The antimicrobial should ideally be active against stationary-phase bacteria as seen in biofilms attached to bone. Drugs that have activity against stationary-phase bacteria include rifampin and fluoroquinolones. Rifampin should never be used as monotherapy because of the common occurrence of a single-step mutation, which confers resistance to the organism and renders rifampin ineffective. In addition, if an oral antibiotic is chosen, agents that have confirmed susceptibility and high oral bioavailability should be used as previously mentioned for DFI. The initial empiric antibiotic choice for DFO should at least include activity against *S. aureus*. Fluoroquinolones are not recommended as single agents for *S. aureus* because of the high resistance rates that have developed to this class on treatment and potential for selection of MRSA.

Therapy Duration

Treatment duration for DFO depends on whether surgical intervention is performed. If all of the infected tissue and bone has been removed (e.g., in a below-the-knee amputation), the recommended treatment duration is for only 2–5 days postoperatively. If there is residual infected tissue, but

not bone, treatment should be continued for 1–3 weeks. If there is residual infected viable bone, treatment should be for 4–6 weeks; practice guidelines recommend 8 weeks for treatment of infections specifically caused by MRSA. If no surgery is performed or there is residual dead bone, at least 6 weeks of antibiotic therapy is recommended.

In a prospective, multicenter, open-label, randomized study, 40 patients with DFO received either 6 or 12 weeks of antibiotics (treated nonsurgically). The primary outcome was remission of osteomyelitis, which was defined as the absence of any local or systemic sign of infection, stabilized or improved radiographic abnormalities on plain radiographs assessed at the end of treatment and 1 year later, and complete sustained healing of the wound. In addition, remission was defined as no recurrence of infection or need for surgery during a posttreatment follow-up of at least 12 months. Twelve patients in the 6-week group (60%) and 14 patients in the 12-week group (70%) achieved the primary outcome (p=0.5). The authors concluded that a 6-week duration of antibiotic therapy is sufficient in patients with DFO for whom antibiotics alone are considered (Tone 2015). Table 1-5 summarizes the recommended treatment durations for DFO.

PREVENTION

Diabetic foot ulcers and infection are a burden to the health care system, but they are avoidable. Preventing this morbidity and mortality involves optimal diabetes management and appropriate foot care.

Diabetes Management

As mentioned in Box 1-1, risk factors for DFIs include the presence of peripheral vascular disease in the affecting limb, poor glycemic control, and loss of protective sensation.

Table 1-5. Antibiotic Therapy Duration for DFO

Severity	Duration
No residual infected tissue after surgery	2–5 days
Residual infected tissue (not bone)	1–3 wk
Residual infected (but viable) bone	4–6 wk (8 wk for MRSA infection)
No surgery, or residual dead bone	≥ 6 wk

Information from: Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Clin Infect Dis 2012;54:132-73.

Glycemic control, as recommended by the American Diabetes Association (ADA); smoking cessation; blood pressure control; and lipid management will help mitigate some of these risk factors for DFIs. Glycemic control can be assessed using A1C. According to the ADA, lowering the A1C to 7% or less helps reduce micro- and macrovascular complications of diabetes. Therefore, for many patients, a reasonable A1C goal is less than 7%. Pharmacists have a responsibility to counsel and educate patients with diabetes about their drugs, optimize diabetes management, and combat polypharmacy. Encouraging patients regarding medication adherence and ownership of their diabetes management will help improve glycemic control. As a result, this will help reduce the incidence of DFUs and DFIs.

Foot Care

The ADA recommends that patients with diabetes perform a daily inspection of their feet for any red spots, blisters, cuts, and swelling. In addition, feet should be washed daily, and interdigital spaces should be dried. Trimming of toenails is also recommended. Walking barefoot is not advised; hence, the patient with diabetes should wear shoes and socks at all times. The ADA recommends an annual comprehensive foot examination by a health care provider. If the patient has a history of foot problems, more frequent checks are recommended.

Practice Points

- About one in four patients with diabetes will have a significant SSTI in their lifetime. These infections are preventable through diligent regular foot care and blood glucose control.
- Risk factors for DFIs are presence of peripheral vascular disease in the affected limb, poor glycemic control, neuropathy, traumatic foot wound, ulceration for more than 30 days, history of recurrent foot ulcers, previous lower-extremity amputation, and improper footwear.
- Not all DFUs are infected. For clinically uninfected wounds, no antimicrobial therapy is required.
- Empiric antimicrobial therapy for DFIs will be determined by severity of infection and patient risk factors for multidrug-resistant organisms such as MRSA and *P. aeruginosa*. For mild infections, empiric therapy should target *S. aureus* and group A *Streptococcus*. For moderate infections, empiric therapy should target MRSA, enteric gram-negative bacilli (not *P. aeruginosa*), and anaerobes. For severe infections, empiric therapy should target MRSA, gram-negative bacilli including *P. aeruginosa*, and anaerobes.
- Mild-moderate DFIs can be treated with oral antibiotics.
- Pathogen identification and susceptibilities may take 3–5 days. Once these results are known, every attempt should be made to narrow the antibiotic spectrum. This is critical because it can reduce cost, avoid toxicity, minimize collateral damage such as C. difficile diarrhea, and prevent the emergence of drug-resistant organisms.
- Good wound care and optimal diabetes management are essential for wound healing.

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case.

A.B. is a 55-year-old man (height 78 inches, weight 46 kg) who presents with a 3-day history of right foot swelling and purulent discharge from a 1-cm ulcer at the base of his foot. The erythema around the ulcer is 0.7 cm. A.B. has a medical history of type 2 diabetes, hypertension, osteoarthritis, and peripheral vascular disease but no known drug allergies. He was hospitalized 3 months ago for total knee arthroplasty but has completed physical therapy and says he is "walking good now." Vital signs and laboratory values include temperature 37.3°C, heart rate 86 beats/minute, respiratory rate 23 breaths/minute, blood pressure 153/92 mm Hg, glucose 151 mg/dL, WBC 11×10^3 cells/mm^3, erythrocyte sedimentation rate 110 mm/hour, and A1C 6%.

1. Which one of the following risk factors places A.B. at greatest risk of DFIs?

    A. Type 2 diabetes
    B. Osteoarthritis
    C. Hypertension
    D. Peripheral vascular disease

2. Which one of the following is best to recommend as an empiric regimen for A.B.?

    A. Cephalexin orally 500 mg every 6 hours plus doxycycline orally 100 mg twice daily × 1 week
    B. Ciprofloxacin orally 750 mg twice daily plus amoxicillin orally 500 mg every 8 hours × 2 weeks
    C. Amoxicillin/clavulanate 875 mg orally twice daily × 1 week
    D. Vancomycin intravenously 15 mg/kg × 1 week

Questions 3–5 pertain to the following case.

D.B. is an 82-year-old m an (weight 101 kg) with a history of type 2 diabetes, peripheral vascular disease, neuropathy, depression, chronic kidney disease, and gout. He presents to the ED with confusion and a temperature of 38.6°C (101.5°F). D.B. stepped on a grandchild's toy about 2 months ago and subsequently developed a 3.5-cm halo of erythema around the wound on the bottom his left foot. The wound is purulent with malodorous drainage. D.B.'s WBC count is 12.3×10^3 cells/mm^3 and SCr is 1.6 mg/dL. He is admitted to the hospital for further treatment with intravenous antibiotics. An MRI of his foot reveals diffuse swelling of the subcutaneous tissue but no inflammation of bone. D.B. is hemodynamically stable.

3. Which one of the following best classifies D.B.'s diabetic foot infection (DFI)?

    A. Mild
    B. Moderate
    C. Severe
    D. Severe with osteomyelitis

4. D.B. undergoes surgical debridement. A Gram stain shows many PMNs, gram-positive cocci in clusters, and gram-negative bacilli. After 5 days of intravenous therapy with vancomycin plus piperacillin/tazobactam, he is clinically improved and ready to be discharged to his primary care provider. Final wound cultures grew MRSA and E.coli. The MRSA is susceptible to daptomycin, linezolid, tetracycline, and vancomycin and resistant to erythromycin, clindamycin, levofloxacin, oxacillin, and trimethoprim/sulfamethoxazole. E.coli is an ESBL producer and is only susceptible to amikacin, gentamicin, meropenem, and piperacillin-tazobactam. It is resistant to ampicillin-sulbactam, all cephalosporins, fluoroquinolones, tobramycin and trimethoprim/sulfamethoxazole. D.B. has Medicare Part A, which pays for intravenous antibiotics administered in an infusion unit if needed. He has transportation for only one trip to the clinic each day. Which one of the following is best to recommend for D.B.?

    A. Daptomycin 400 mg intravenous daily and ceftriaxone 2 g intravenously daily
    B. Vancomycin 1.5 g intravenously daily and ertapenem 1 g intravenously daily
    C. Linezolid 600 mg orally once daily and gentamicin intravenously 1.5 mg/kg every 12 hours
    D. Doxycycline 100 mg orally twice daily and moxifloxacin 400 mg orally once daily

5. Which one of the following treatment durations is best to recommend for D.B.?

    A. 10 days
    B. 3 weeks
    C. 6 weeks
    D. 3 months

6. A prospective randomized controlled trial examined amputation rates after mild DFIs caused by MRSA were treated with either trimethoprim/sulfamethoxazole or clindamycin. Amputation rates at day 30 were 4% for trimethoprim/sulfamethoxazole (n=45) and 4.5% for clindamycin (n=44) (p=0.97, 95% CI, 0.5 [-1.4 to 1.8]). Which one of the following best describes the number needed to treat with trimethoprim/sulfamethoxazole to prevent one amputation compared with clindamycin?

    A. 100
    B. 200
    C. 50
    D. Not applicable

7. A 51-year-old man with diabetes presents to the clinic with a left foot abscess. The abscess is drained, and cultures show gram-positive cocci in clusters. The patient states that he would prefer not to take daily infusions

because of his work schedule. Which one of the following is the best antimicrobial regimen to recommend for this patient?

- A. Oritavancin
- B. Tigecycline
- C. Telavancin
- D. Dalbavancin

Questions 8–10 pertain to the following case.

D.F. is a 67-year-old woman who presents to the clinic with complaints of a sore and slightly swollen foot. She checks her feet daily, and 4 days ago, she noticed a stone in her shoe. On inspection today, she has a 1-cm halo of erythema around the ulcer on the bottom of her right foot. It is indurated and red but not weeping. D.F. is embarrassed by the state of her long nails, saying, "I don't visit a salon or anything fancy like that for pedicures." Her temperature is 37.4°C (99.3°F) and she is in no apparent distress. D.F. takes metformin and glipizide for diabetes, lisinopril for hypertension, and aspirin for cardiovascular risk reduction. She has otherwise been healthy for the past year; her A1C is 6.8%.

8. Which one of the following best classifies D.F.'s diabetic foot ulcer (DFU)?

- A. Uninfected
- B. Mild
- C. Moderate
- D. Severe

9. Which one of the following is best to recommend for treatment of D.F.'s DFU?

- A. Local wound care
- B. Trimethoprim/sulfamethoxazole 800/160 mg orally twice daily
- C. Ciprofloxacin 500 mg orally twice daily
- D. Cephalexin 500 mg orally four times daily

10. During a follow-up visit, D.F. would like to know what she might do to prevent future infections like this. Which one of the following education points is best for D.F.?

- A. Inspect feet weekly
- B. Wash feet daily, dry interdigital spaces, and trim toenails
- C. Improve glycemic control
- D. Wear socks with her shoes

11. An 81-year-old man has a medical history of type 2 diabetes, depression, chronic bronchitis, and heart failure. He has had several hospital admissions in the past year for chronic obstructive pulmonary disease exacerbations, including a 4-day hospital stay just 2 weeks ago. Today, he presents with cellulitis of the left foot surrounding the chronic ulcer on the heel. The erythema around the ulcer is 0.5 cm. The probe-to-bone (PTB) test is negative, and his vital signs and blood tests are within normal limits. His home drugs include insulin glargine, insulin aspart, citalopram, albuterol, ipratropium, furosemide, benazepril, and metoprolol succinate. Which one of the following is the best antimicrobial therapy to recommend for this patient's DFI?

- A. Levofloxacin 750 mg orally daily
- B. Cephalexin 500 mg orally three times daily
- C. Clindamycin 600 mg orally three times daily
- D. Linezolid 600 mg orally twice daily

12. A 45-year-old man with type 1 diabetes and gastroesophageal reflux disease (GERD) steps on a nail while working on the family farm. His laboratory results are as follows: WBC 14×10^3 cells/mm^3, SCr 0.8 mg/dL, erythrocyte sedimentation rate 65 mm/hour, and CRP 1.5 mg/L. An MRI reveals acute changes in the bottom of his calcaneus bone consistent with osteomyelitis. The patient receives broad-spectrum antibiotics and a tetanus booster with the tetanus, diphtheria, and acellular pertussis vaccine. The next day, surgical debridement occurs, and a deep tissue specimen is sent to the laboratory. The Gram stain shows many PMNs and gram-positive cocci in clusters. The patient has a history of allergic reaction to penicillin (anaphylaxis). He takes insulin for his diabetes and omeprazole for GERD. After 1 week of taking vancomycin the patient is clinically improving, but his SCr concentration rises to 1.8 mg/dL with an elevated vancomycin trough of 28 mcg/mL. The physician decides to change the regimen to daptomycin. Which one of the following daptomycin dosing regimens is best to recommend for outpatient parenteral antimicrobial therapy in this patient?

- A. 4 mg/kg daily
- B. 6 mg/kg daily
- C. 8 mg/kg daily
- D. 10 mg/kg daily

13. An 89-year-old woman presents with a medical history of atrial fibrillation, type 2 diabetes, osteoarthritis, and general anxiety disorder. Her home drugs include amiodarone, warfarin, metformin, fluoxetine, calcium carbonate with vitamin D, as-needed acetaminophen, and a multivitamin. The patient is in clinic with a DFI. She has been treated for the last week with amoxicillin-clavulanate. Cultures are now growing MRSA and *E. coli*. The patient's MRSA is susceptible to clindamycin, trimethoprim/sulfamethoxazole, and linezolid while being resistant to tetracycline. Her *E. coli* is resistant to amoxicillin/clavulanate, tetracycline, and trimethoprim/sulfamethoxazole, but it is susceptible to cephalexin and levofloxacin. The patient's next appointment at anticoagulation clinic is in 2 weeks. Her QTc was 501 milliseconds the last time it was checked. The physician would like to start her on oral antibiotics. Which one of the following is best to recommend for this patient?

A. Doxycycline 100 mg orally once daily plus levofloxacin 500 mg orally daily
B. Trimethoprim/sulfamethoxazole 1 double-strength tablet orally twice daily
C. Clindamycin 450 mg orally four times daily plus cephalexin 500 mg orally four times daily
D. Linezolid 600 mg orally twice daily plus levofloxacin 750 mg orally daily

Question 14 and 15 pertain to the following case.

D.L. is a 45-year-old man with diabetes who presents with purulent drainage from his left heel for 4 days. He states he hit his foot on a rock while swimming in a lake. He self-medicated with topical triple antibiotic ointment, with no improvement in symptoms. D.L. reports chills, fevers, left foot swelling, and pain on touch. His WBC is 14×10^3 cells/mm^3, temperature 100°F, SCr 1.0 mg/dL, and erythrocyte sedimentation rate 12 mm/hour. The physician wants to rule out osteomyelitis, then treat for common foot and water pathogens.

14. Which one of the following would best assist in determining whether D.L. has osteomyelitis?

    A. MRI of left foot
    B. PTB test
    C. Radiography of left foot
    D. Wound greater than 5 cm

15. Nothing is identified on D.L.'s Gram stain or culture, and osteomyelitis is ruled out. Which one of the following is the best antimicrobial regimen to recommend for D.L.?

    A. Moxifloxacin 400 mg orally daily
    B. Amoxicillin/clavulanate 875 mg orally twice daily
    C. Linezolid 600 mg orally twice daily plus ciprofloxacin 750 mg orally twice daily
    D. Vancomycin (goal trough 15–20 mcg/mL) plus gentamicin 5 mg/kg every 8 hours

16. A study will compare outcomes in patients with mild DFIs. Patients will be randomized to receive either clindamycin or linezolid for 2 weeks. The investigators want to enroll 100 patients in each group. The primary end point is the proportion of patients who have a clinical cure at the end of 2 weeks. Which one of the following is the best statistical test for this type of investigation?

    A. Chi-square test
    B. Paired t-test
    C. Student t-test
    D. Analysis of variance

Questions 17 and 18 pertain to the following case.

T.D., an 81-year-old man with diabetes, received a new diagnosis of right foot osteomyelitis after he developed a chronic nonhealing wound ulcer on his right great toe 5 weeks ago. He had taken cephalexin for 2 weeks before admission. T.D.

undergoes wound debridement but not amputation; therefore, the residual infected bone remains. Bone samples were taken during surgery and sent for cultures. The following organisms and susceptibilities were obtained:

Staphylococcus epidermidis

Drug	Susceptibilities
Clindamycin	R
Daptomycin	S
Doxycycline	R
Linezolid	S
Oxacillin	R
Rifampin	S
Trimethoprim/ Sulfamethoxazole	R
Vancomycin	S

Klebsiella oxytoca

Drug	Susceptibilities
Ampicillin	R
Amoxicillin/clavulanate	S
Cefazolin	R
Cefoxitin	R
Ceftriaxone	S
Ertapenem	S
Gentamicin	S
Levofloxacin	R
Trimethoprim/ Sulfamethoxazole	R

17. Which one of the following is best to recommend for T.D.?

    A. Ertapenem intravenously 1 g every 24 hours for 4 weeks
    B. Linezolid 600 mg orally twice daily plus ceftriaxone intravenously 2 g every 24 hours for 10 weeks
    C. Vancomycin intravenously (goal trough 15–20 mcg/ mL) plus ceftriaxone intravenously 2 g every 24 hours for 6 weeks
    D. Daptomycin intravenously 6 mg/kg every 24 hours plus amoxicillin/clavulanate 875 mg orally twice daily for 2 weeks

18. After appropriate therapy is selected, T.D.'s wound is slow to heal. The physician would like to know more about adjunctive therapy that can help prevent amputation. Although not recommended for routine use, which one of the following therapies would be most appropriate for T.D.?

A. Granulocyte colony-stimulating factor
B. Hyperbaric oxygen therapy
C. Bioengineered skin equivalent
D. Platelet-derived growth factor

Questions 19 and 20 pertain to the following case.

T.Z. is an 88-year-old man with a long-standing history of vascular insufficiency, diabetes mellitus (A1C 9%), hypertension, and obesity. He presents to the ED with erythema and warmth and swelling of his left heel for about 4 days. On examination, there is a 1-cm halo of erythema around the heel ulcer. T.Z. has no fever or leukocytosis.

19. Which one of the following is best to recommend for T.Z.'s DFI?

A. Cephalexin 500 mg orally four times daily
B. Amoxicillin 875 mg orally twice daily
C. Doxycycline 100 mg orally twice daily
D. Trimethoprim/sulfamethoxazole 1 double-strength tablet orally twice daily

20. Which one of the following is best to recommend as the therapy duration for T.Z.'s DFI?

A. 7 days
B. 21 days
C. 28 days
D. 42 days