Treatment of Diabetic Foot Infections

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Diabetes is a major health concern both globally and within the United States. It is estimated that >37 million people have diabetes in the United States alone (1). Complications from diabetes, such as diabetic foot infection (DFI), continue to be a primary contributor of morbidity and mortality. In 2018, there were 154,000 hospital discharges for patients with diabetes and a lower-extremity amputation (1).

Etiology

"Diabetic foot infection" is a broad term that refers to a constellation of conditions involving the feet of people with diabetes. DFIs arise when there is an initial trauma to the foot such as calluses, dry skin, or an unperceived repetitive injury. This trauma compromises the skin integrity and, in the presence of ischemia and peripheral neuropathy, can further progress to an ulcer or a deeper infection involving skin structures or even bone (2).

Causative Organisms

Classically, DFIs have been characterized as polymicrobial. Because of the presence of commensal bacteria and frequent contamination of longstanding wounds, causative organisms can be difficult to determine. A recent meta-analysis examined the microbiology of DFIs and found that *Staphylococcus aureus* (23.4%) was the most common organism identified by either foot swab or biopsy, followed by *Escherichia coli* (11.5%) and *Pseudomonas* species (spp.) (11.1%) (3).

Therapy

In addition to preventive care, DFI treatment includes proper wound care, use of antimicrobials, and surgical therapy. Preventive care and antimicrobial therapy will be discussed further below.

Preventive Therapy

The American Diabetes Association's *Standards of Medical Care in Diabetes* guidelines recommend preventive foot care as integral to a successful diabetes management strategy. Some recommended prevention techniques include provision of patient education regarding daily foot examinations, use of properly fitting shoes, avoidance of walking barefoot, and efforts to keep feet clean and dry and to trim toenails (4).

Antimicrobial Therapy

Antimicrobial therapy is determined by the severity of the DFI and risk factors for multidrug resistant organisms such as methicillin-resistant *S. aureus* (MRSA) and *Pseudomonas aeruginosa*. MRSA risk factors include prior MRSA infection or colonization, high local prevalence of MRSA, and severe infection (5). Although *P. aeruginosa* can be a colonizer of DFIs, there are certain characteristics that may put patients at higher risk for *P. aeruginosa* infections. These include high local prevalence of *Pseudomonas*, warm climate, frequent exposure of the foot to water, severe infection, and failure of a previous therapy with an antibiotic lacking *Pseudomonas* activity (5).

Mild DFIs involve a local infection of the skin and subcutaneous tissue with no systemic signs of infection and erythema <2 cm (5). Most mild infections can be treated with oral, relatively narrow-spectrum agents against the most likely causative pathogens such as aerobic gram-positive cocci (*Staphylococcus* spp. and *Streptococcus* spp.). In patients without risk factors for MRSA, recommended antibiotics include dicloxacillin, cephalexin, amoxicillin-clavulanate, clindamycin, or levofloxacin (5). In patients with MRSA risk factors, oral anti-MRSA agents such as trimethoprim/sulfamethoxazole or doxycycline are recommended (5).

Moderate to severe DFIs are characterized by local infection with erythema >2 cm or involving structures deeper than skin and subcutaneous tissues in the absence (moderate) or presence (severe) of two or more systemic signs and symptoms (i.e., temperature >38°C or <36°C, heart rate >90 bpm, respiratory rate >20 breaths/minute, and white blood cell count

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>12,000 or <4,000 cells/μL) (5). Antibiotics may be oral or intravenous, with the latter preferred in severe infections. In patients without risk factors for *Pseudomonas* or MRSA, treatment options include ampicillin-sulbactam, ertapenem, cefoxitin, ceftriaxone, moxifloxacin, tigecycline, levofloxacin, or ciprofloxacin combined with clindamycin (5). If the patient is at risk for *Pseudomonas*, then piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, or imipenem-cilastatin are treatment options (5). For patients with MRSA risk factors, vancomycin, daptomycin, or linezolid may be used (5).

Duration of therapy is determined by the severity and extent of the DFI. In patients with mild infections, antimicrobial therapy lasts 1–2 weeks; the duration of therapy is 2–3 weeks in patients with moderate to severe infections. Longer durations of treatment are recommended for DFIs that involve bone (5).

Commentary

Since the last publication of the Infectious Diseases Society of America's guidelines for DFI treatment (5), new antimicrobials have been approved for complicated skin and skin structure infections, with limited clinical trial data for DFIs. Although real-world experience has been lacking for newer antimicrobials, recent data have been published for dalbavancin (6) and ceftaroline (7).

Dalbavancin is an intravenous long-acting glycopeptide with antimicrobial activity against many gram-positive pathogens such as *S. aureus* (including MRSA), *Streptococcus* spp., and vancomycin-susceptible *Enterococcus* spp. (6). The average wholesale price (AWP) of dalbavancin is $2,012.40 for 500 mg (8). A course of therapy for dalbavancin (1,500 mg) has an AWP of $6,037.20. A recent, retrospective study of 23 patients with DFIs in Spain demonstrated that dalbavancin was well tolerated and provided high clinical cure rates (87%, 95% CI 64.15–93.32%) (6).

Ceftaroline is an intravenous fifth-generation cephalosporin with activity against gram-negative and gram-positive organisms such as *S. aureus* (including MRSA) and *Streptococcus* spp. (7). The AWP for ceftaroline is $266.88 per 600 mg (8). For a patient with normal renal function, a 10-day course of therapy has an AWP of $5,337.60. A retrospective cohort study that included 87 patients with diabetes and gram-positive osteomyelitis concluded that patients who received treatment for primary osteomyelitis of the foot with ceftaroline experienced similar clinical cure rates regardless of whether they had diabetes (89.4% [59 of 66] vs. 88.9% [16 of 18]) (7). Although these data for both dalbavancin and ceftaroline offer some additional therapeutic options for DFIs, more robust clinical data are still needed.

The global coronavirus disease 2019 (COVID-19) pandemic has created opportunities to provide services to a wider range of patients through telehealth (9). In a study examining outcomes of DFI during the COVID-19 lockdown in India, patients with DFIs were provided telehealth consultations and virtual triaging using a multidisciplinary team approach and were then compared with a historical control group (9). The authors concluded that there was no statistical difference between telehealth visits and face-to-face controls in wound closure or reduction (78.4 vs. 76.0%, $P = 0.318$), amputation (5.4 vs. 6.8%, $P = 0.191$), or mortality (3.8 vs. 4.3%, $P = 0.532$) (9).

Current standards of care for diabetes recommend a multidisciplinary approach to DFI treatment (4). Although there is no specific recommendation regarding the types of professionals comprising such teams, multidisciplinary team approaches have been shown to improve patient outcomes such as reducing amputations associated with DFIs (10).

Bottom Line

Complications associated with DFIs continue to be a source of morbidity and mortality for many patients with diabetes. Preventive measures, appropriate antimicrobial selection, and a multidisciplinary team approach appear to reduce complications and improve outcomes in patients with DFIs.

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