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Management of Diabetic Foot Infections with Appropriate Use of Antimicrobial Therapy

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Abstract

Up to 25% of patients with diabetes will develop a foot ulcer during their lifetime with a 50-70% recurrence rate over the ensuing 5 year. Additionally more than 50% of patients with a diabetic foot ulcer (DFU) develop a diabetic foot infection (DFI). DFI remains a challenge to manage because of coexisting immunopathy. Antibiotic therapy is the main stay of treatment for patients with deep and surrounding tissue infection. A multidisciplinary approach is required with the focus on the comprehensive patient assessment, vascular assessment with revascularization, proper offloading devices and use of appropriate antimicrobials. Wound care professionals have a unique position to lessen the inappropriate use of antimicrobials.

Keywords: Diabetic foot infections; Antimicrobial therapy; Diabetes

Introduction

Diabetes mellitus is a prevalent disease worldwide where its prevalence in developed countries is 6 to 11% while in developing countries it may reach up to 30%. Although its prevalence increases with age, it is becoming more prevalent in working age group [1-3]. Diabetic foot ulcers (DFUs) are commonly encountered as a complication of diabetes where its lifetime risk can reach up to 25% [4].

Diabetic foot infections (DFIs) commonly start from infected DFUs where more than half of DFUs get infected. However, DFIs can occur without pre-existing DFUs. All wounds are contaminated from surface bacteria. When the bacteria attach to tissue and multiply, a state of colonization exists where host resistance is still predominant. As soon as colonized bacteria cause local damage to the tissue, a state of localized infection is created often termed critical colonization. The high bacterial count in the critical colonization stage may delay healing and lead to overt deeper and surrounding tissue infection when host resistance is compromised [5].

DFIs are associated with increased morbidity, mortality, rate of hospitalization, amputation, and cost. They are also associated with a significant decline of individuals' functional status and their psychological well being [6,7]. There is a tenfold increase in rate of hospitalization with bone and soft tissue infections in individuals with diabetes than without diabetes [8-10]. Worldwide, lower extremity amputation is mainly due to diabetes where the risk of a lower extremity amputation is twenty fold increased in patients with diabetes and 25-90% of amputations worldwide is associated with diabetes [11,12].

It is easy to imagine the current healthcare cost burden from DFIs and the need for improved patient quality of life and decreased healthcare costs with early diagnosis and management of DFIs. The thoughtful use of systemic antimicrobial s is important for all health care professionals since their use is one of the main treatment elements of DFIs. Wound care professionals need to balance the concern regarding overuse of systemic antimicrobials with improved chronic wound outcomes with longer-term antimicrobial therapy. This article reviews antimicrobial therapy as a key part in the management of DFIs.

Management of the Diabetic Foot Infections

DFUs are divided to diabetic neurotrophic foot ulcers and diabetic neuroischemic foot ulcers with the occasional patient having distal ischemia without neuropathy. The approach to DFIs is different in the ischemic foot. Although all diabetic neurotrophic ulcers have some degree of ischemia, neuroischemic ulcers often are less likely to respond to appropriate systemic therapy. Large vessel ischemia (macrovascular disease) often requires vascular procedures for successful control of infection and ulcer healing [13-17].

The management of DFIs is challenging with high cost for both the patient and the health care system. A multi-professional approach with attention to local and systemic factors is required for the management of DFI [18,19]. A holistic approach to the whole patient is critical in the management of DFUs and DFIs along with optimizing local wound care. Control of blood sugar is important. As each 1% drop in HbA1-c is associated with 37% risk reduction in micro vascular disease such as neuropathy [20]. There is also the need to control of hypertension and the associated risk of cardiovascular and kidney disease [20]. A comprehensive assessment including history and physical exam is required for all patients with concerns regarding activities of daily living, the presence of depression, as well as alcohol consumption and smoking.

The evidence of appropriate management of DFIs depends on early detection and prescription of pathogen-appropriate antimicrobial therapy. The clinical signs and symptoms of the infections are key to the diagnosis but the diabetes-associated challenge of immunopathy and neuropathy especially with uncontrolled diabetes may mask the symptoms of infection. The manifestations of infections such as erythema or swelling are not specific to DFIs and can occur in other

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conditions. For example, acute degenerative neuroarthropathy which is characterized by a progressive deterioration of weight-bearing joints, usually in the foot or ankle, can clinically mimic cellulitis and presents as erythema, edema and elevated temperature of the foot [7].

Although the diagnosis of the infection is clinical, the decision for antimicrobial therapy is often erroneously based on laboratory culture reports that may have identified resistant organisms or recent consensus guidelines. The culture techniques including superficial bacterial swab may detect resistant organisms but may identify surface contamination or colonizers but not necessarily pathogens. A culture from curetted tissue or punch biopsy would provide more accurate information of the deep and surrounding ulcer compartment. The Levine bacterial swab technique includes:

- Cleaning the wound with saline or water compress.
- Identifying a normal appearing area in the wound base to apply the swab.
- Press firmly to extract fluid and rotate 360 degrees.
- If the surface is too dry for an adequate swab, the cotton tip can be placed in the transport media first to moisten the surface prior to swabbing the wound.

The microbiology of DFIs is not the same for all infections. It depends on several factors that include the duration of the infection, setting of acquiring the infection, prior history of infection, prior use of antimicrobial agents, presence of ischemia, and geographic area. Aerobic Gram-positive cocci, especially *Staphylococcus aureus*, are the most common cause of DFIs. Individuals with chronic foot ulcers and previous antimicrobial therapy often have infections with both gram positive and gram-negative organisms and often become co-infected over time with anaerobic pathogens [19].

Antimicrobial Therapy for the Diabetic Foot Infections

Antimicrobial therapy is one of the main treatment arms of DFIs. There are two types of antimicrobial therapy for DFIs: empiric and directed therapy. Empiric antimicrobial therapy should be started after taking all appropriate cultures. However, in patients with severe DFIs and hemodynamic instability, empiric antimicrobial therapy should be started as early as possible, even before taking appropriate cultures if it will be delayed. The choice of empiric antimicrobial therapy is based mainly on the expected pathogens, risk of antimicrobial resistance, and the severity of the infection (Table 1). The choice of directed antimicrobial therapy is mainly based on the isolated organisms and their susceptibility testing results and response to the antimicrobial [7]. Directed antimicrobial therapy should be as narrow-spectrum as possible and cost-effective as well. Antimicrobial's that are associated with high risk of Clostridium difficile infection (CDI) should be avoided if possible (ceftriaxone, fluoroquinolones, clindamycin). CDI should be suspected if the patient has had more than 3 unformed bowel movements in the previous 24 hours, fever, abdominal pain, and leukocytosis [21].

There is no evidence for the superiority of one type of antimicrobial therapy over another due to lack of high-quality DFIs clinical studies. However, knowing the antimicrobials and their main characteristics is important to guide the choice of treatment for patients with DFIs (Table 2). Antimicrobials should be initiated parenterally for moderate and severe infections and then continued for the whole course of treatment if there is no alternative oral antimicrobial (due to resistant organisms or poor tissue penetration). Oral antimicrobial therapy can administer initially for mild to moderate infections and as a step down for moderate and severe infections if the infection is responding to initial parenteral antimicrobial therapy. The best antimicrobial therapy results occur if the isolated organisms are susceptible to prescribed antimicrobial with good bioavailability and tissue penetration. Clinicians should always remember that cultures may not always identify all the pathogens and unless special precautions are taken, anaerobes present in the wound may not be represented in the bacterial culture result. Other consideration that should be taken when selecting antimicrobial for treatment of DFIs include frequency of administration, gastrointestinal tract absorption function, potential adverse effects, drug interactions, cost, and patient's history of allergy and comorbid conditions such as renal and hepatic disease [14,22].

Antimicrobial therapy should not be used prophylactically to treat uninfected diabetic foot ulcers since it does not improve healing or prevent infections but may further drive resistance and adverse effects [23]. There are two types of antimicrobial agents than can be used in the treatment of DFIs: topical and systemic antimicrobials. The presence of bacteria in the wounds may be detrimental with critical colonization often amenable to topical antimicrobials and the deep and surrounding infection requiring systemic antimicrobial agents.

Antimicrobial resistance is a growing problem worldwide. The main resistant organisms that involved in DFIs are so called the ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa, and enterobacteriaceae*). The prevalence of MRSA in DFIs is approximately 5-30% and its incidence is increasing. MRSA is associated with poor wound healing and a higher risk of lower extremity amputation in patients with DFIs. Risk factors for MRSA infection include previously colonization or infection with MRSA, household contact of patient with MRSA, exposure to a unit/area with an MRSA outbreak, hemodialysis, comorbid conditions, hospitalization, surgery, admission to ICU, antimicrobial exposure (fluoroquinolones), and in communities where the prevalence of MRSA infection exceeds 10-15% [24-26]. More recently, there is an increasing presence of antimicrobial resistant Gram-negative organisms from DFIs. Risk factors for infections with antimicrobial-resistant organisms include previous colonization or infection with the same organism, contact of a known case of same organism, elderly, patients who have been soaking their feet, hospitalization, ICU admission, surgery, immunocompromised status, prior antimicrobial therapy (fluoroquinolones, cephalosporins, carbapenems), recurrent urinary tract infection, hemodialysis, receipt of care in a hospital on the U.S. eastern seaboard region (e.g., New York City) or in Greece, middle east or the Indian subcontinent in the past 12 months [27,28]. Finally, antimicrobial resistance is an evolving problem. Therefore, ongoing surveillance for antimicrobial -resistant organisms is vital for the treatment of DFIs and optimization of infection-control measures to prevent their spread.

The treatment duration of DFIs with antimicrobial is based primarily on response to treatment (good response is indicated by resolution of systemic symptoms and signs (such as fever) associated with the infection, improvement/resolution of local symptoms and signs of infection (redness, drainage), healing of the wound, and decreasing inflammatory markers including ESR and CRP, type and extent of the infection, the vascular status of the infected foot and its treatment, and type of surgical treatment. Treatment for 1 to 2 weeks is usually adequate for mild DFI while moderate and severe soft tissue infections

may require treatment for 2 to 4 weeks or longer. The recommended duration of antimicrobial therapy for diabetic foot osteomyelitis (DFO) has traditionally been 4 to 6 weeks but can be extended based beyond this duration based on the response, presence of ischemia, and type and extents of surgical treatment [19].

Superficial soft-tissue infection can be managed with topical antimicrobials, oral or parenteral antimicrobial agent and with or without debridement. Deeper soft-tissue or bone infections may require hospital admission with parenteral antimicrobial agents and serial surgical debridement/decompression. Deep soft-tissue infections of are often polymicrobial with gram-positive species as well as gram-negative bacteria, whereas superficial soft-tissue infection bone infections are usually monomicrobial [29].

Outpatient parenteral antimicrobial therapy (OPAT) facilitates treatment of DFIs and DFO as outpatient. However, OPAT requires patient selection and evaluation; antimicrobial selection including efficacy, route, frequency, dosage, duration, and clinical and laboratory monitoring for adverse effects (vancomycin trough) and type of venous access. The need for OPAT should be determined by a physician who is experienced in treating DFIs. The infection should be controlled and stabilized and all necessary surgical procedures should have been performed before starting OPAT. Ongoing maintenance debridement may be required to accelerate healing. Patients or caregiver's require adequate counselling on the care of wounds, venous access, and adverse effects of antimicrobial therapy and the need to report adverse events to their provider. It is preferable to choose an antimicrobial agent that is administered once or twice daily without compromising the clinical efficacy [30]. However, it is recommended to use cefazolin given 3 or 4 times daily over vancomycin given once or twice daily for DFIs, particularly for osteomyelitis, due to methicillin-sensitive *S. aureus* [25]. The first dose of antimicrobial should be administered in a supervised setting equipped for emergencies to deal with any serious reactions such as anaphylaxis (e.g. Outpatient medical clinic or emergency department). Treating physician should be familiar with complications of venous access such phlebitis, bloodstream infections, thrombosis of the veins, clotting of the catheter, pulmonary emboli, migration of the catheter tip, erosion of the catheter through the vein [31].

Biofilms [32] are produced by bacteria often between two surfaces of different viscosity such as slough on the surface of a wound. A biofilm is a colony of bacteria that excrete a glycocalyx for protection from antimicrobial agents, and allows a symbiotic relationship with the community of bacteria so that some organisms may be in a relatively protected resting state [32]. The use of antimicrobial therapy alone (without proper debridement) may reverse the signs of infection but often does not penetrate the outer protective covering of the biofilm and fails to kill the biofilm-associated bacteria. The treatment strategy of biofilm includes sharp excision of the wound to disrupt the biofilm, with immediate antimicrobial therapy to prevent its rapid reformation [33].

Type of infection	Clinical manifestations	Empiric antibiotics
Infected ulcer without cellulitis IDSA classification: Mild	At least two of the classic signs or symptoms of a host inflammatory response (erythema, swelling, warmth, tenderness, pain) or purulent drainage without fever. Other manifestations include nonpurulent secretions, friable or discolored granulation tissue, undermining of the wound edges, or a foul odor.	Topical antiseptic or antimicrobial agents
Infected ulcer with cellulitis IDSA classification: Moderate*	Symptoms and signs of infected ulcer with erythema(localized when extending ≤ 2 cm around the ulcer and generalized when extending >2 cm), swelling, pain/tenderness, and warmth of the affected area surrounding the ulcer with/without systemic symptoms and signs such as fever.	**No risk of MRSA infection:** Dicloxacillin 500 mg po q6h Cephalexin 500 mg po q6h Clindamycin 300 mg-450 mg po q6h or clindamycin 600 mg iv q8h Nafcillin/Cloxacillin 1-2g iv q6h Cefazolin 1-2 g iv q8h Ceftriaxone 1-2 g iv q24h Moxifloxacin 400 mg po/iv q24 Levofloxacin 500 mg po/iv q24 **High risk of MRSA infection †:** Clindamycin 300 mg-450 mg po q6h or clindamycin 600 mg iv q8h Trimethoprim/Sulfamethoxazole 160/800 mg tablets po bid Minocycline/doxycycline 100 mg po q12h Vancomycin 15 mg/kg iv q12h Linezolid 600 mg po/iv q12h Daptomycin 4 mg/kg iv q24h Telavancin 10 mg/kg q24h
Cellulitis without ulcer IDSA classification: Moderate*	Erythema, swelling, pain/tenderness, and warmth of the affected area with/without signs of systemic symptoms and signs such as fever	**No risk of MRSA infection:** Dicloxacillin 500 mg po q6h Cephalexin 500 mg po q6h Clindamycin 300 mg-450 mg po q6h or clindamycin 600 mg iv q8h Nafcillin/Cloxacillin 1-2g iv q6h Cefazolin 1-2 g iv q8h Ceftriaxone 1-2 g iv q24h Moxifloxacin 400 mg po/iv q24 Levofloxacin 500 mg po/iv q24 **High risk of MRSA infection** †: Clindamycin 300 mg-450 mg po q6h or clindamycin 600 mg iv q8h Trimethoprim/Sulfamethoxazole 160/800 mg tablets po bid Minocycline/ doxycycline 100 mg po q12h Vancomycin 15 mg/kg iv q12h Linezolid 600 mg po/iv q12h Daptomycin 4 mg/kg iv q24h Telavancin 10 mg/kg q24h

Erysipelas with/without an ulcer IDSA classification: Moderate*	Intense erythema, induration and sharply demarcated borders with/without systemic symptoms and signs such as fever.	Cephalexin 500 mg po q6h Clindamycin 300 mg-450 mg po q6h or clindamycin 600 mg iv q8h Cefazolin 1-2 g iv q8h Ceftriaxone 1-2 g iv q24h
Deep soft tissue infection IDSA classification: Moderate*	Purulent foul-smelling discharge from the ulcer, Including abscess, severe pain, systemic symptoms and signs such as fever, malaise, nausea, and metabolic instability such as ketoacidosis.	**No risk of MRSA infection:** Amoxicillin/clavulanate 500-875 mg po q8h/q12h Ampicillin/sulbactam 3g iv q6h Cefazolin 1-2 g iv q8h plus clindamycin 300-450 mg po q6h, clindamycin 600 mg iv q8h, or metronidazole 500 mg po/iv q8-12 h Ceftriaxone 1-2 g iv q24h plus clindamycin 300-450 mg po q6h, clindamycin 600 mg iv q8h, or metronidazole 500 mg po/iv q8-12h Levofloxacin§500 mg po/iv q24 plus clindamycin 300-450 mg po q6h, clindamycin 600 mg iv q8h, or metronidazole 500 mg po/iv q8-12h Moxifloxacin 400 mg po/iv q24h Ceftazidime §1-2 g iv q 8 h plus clindamycin 300-450 mg q 6 h or clindamycin 600 mg iv q8h Cefepime§2 g iv q12h plus clindamycin 300-450 mg po q 6 h, clindamycin 600 mg iv q8h ,or metronidazole 500 mg po/iv q8-12h Piperacillin/tazobactam §3.375/4.5 g iv q6-8h Ertapenem 1 g iv q24 h Imipenem/cilastin §500 mg iv q6h Meropenem §500-1000 mg iv q6-8 h Doripenem §500 mg iv q8h Tigecycline 100 mg IV loading dose followed by 50 mg IV q12h Ceftaroline 600 mg iv q12h **High risk of MRSA infection** †: Amoxicillin/clavulanate 500-875 mg po q8h/q12h plus either Trimethoprim/ Sulfamethoxazole 160/800 mg tablets po bid or doxycycline 100 mg po q12h Ceftriaxone 1-2 g iv q24h plus metronidazole 500 mg po/iv q8-12h plus vancomycin 15 mg/kg iv q12h Cefepime§ 2 g iv q12h plus metronidazole 500 mg po/iv q 8-12h plus vancomycin 15 mg/kg iv q12h Ceftazidime §1-2 g iv q 8h plus metronidazole 500 mg po/iv q 8-12 h plus Vancomycin 15 mg/kg iv q12h Piperacillin/tazobactam §3.375/4.5 g iv q6-8 h plus vancomycin 15 mg/kg iv q12h Ertapenem 1 g iv q24h plus vancomycin 15 mg/kg iv q12h Imipenem/cilastin§ 500 mg iv q 6 h plus vancomycin 15 mg/kg iv q12h Meropenem §500-1000 mg iv q 6-8h plus vancomycin 15mg/kg iv q12h Doripenem §500 mg iv q8 h plus vancomycin 15 mg/kg iv q12h Tigecycline 100 mg IV loading dose followed by 50 mg iv q12h Ceftaroline 600 mg iv q12h
Necrotizing fasciitis/ myonecrosis IDSA classification: Severe	Fever, severe pain, systemic toxicity (delirium, diaphoresis, tachycardia, hypotension), gas in the tissue, and metabolic instability (acidosis, dysglycemia, electrolyte abnormalities, worsening azotemia, abnormal liver function tests).	**No risk of MRSA infection:** Ceftriaxone 1-2 g iv q24h plus clindamycin 600 mg iv q8h, or metronidazole 500 mg iv q8-12h Levofloxacin§500 mg po/iv q24 plus clindamycin 600 mg iv q8h or metronidazole 500 mg iv q8-12h Ceftazidime §1-2 g iv q 8 h plus clindamycin 600 mg iv q8h Cefepime§2g iv q12h plus clindamycin 600 mg iv q8h or metronidazole 500 mg iv q8-12h Piperacillin/tazobactam §3.375/4.5 g iv q6-8h Ertapenem 1g iv q24h Imipenem/cilastin §500 mg iv q6h Meropenem §500-1000 mg iv q6-8h Doripenem §500 mg iv q8h Tigecycline 100 mg IV loading dose followed by 50 mg IV q12h **High risk of MRSA infection** †: Cefepime§ 2g iv q12h plus metronidazole 500 mg iv q 8-12h plus vancomycin 15mg/ kg iv q12h Ceftazidime §1-2 g iv q 8h plus metronidazole 500 mg iv q 8-12h plus Vancomycin 15mg/kg iv q12h Piperacillin/tazobactam §3.375/4.5g iv q6-8 h plus vancomycin 15mg/kg iv q12h Ertapenem 1g iv q24h plus vancomycin 15mg/kg iv q12h Imipenem/cilastin§ 500 mg iv q 6 h plus vancomycin 15mg/kg iv q12h Meropenem §500-1000 mg iv q 6-8h plus vancomycin 15mg/kg iv q12h Doripenem §500 mg iv q8 h plus vancomycin 15mg/kg iv q12h Tigecycline 100 mg IV loading dose followed by 50 mg iv q12h

Septic arthritis IDSA classification: Moderate*	Swollen, warm, red and tender joint, painful range of motion, systemic symptoms and signs such as fever, elevated inflammatory markers (CRP, ESR), and usually with concomitant soft tissue and bone involvement.	**No risk of MRSA infection:** Cefazolin 1-2 g iv q8h Ceftriaxone 1-2 g iv q24h Moxifloxacin 400 mg po/iv q24 Levofloxacin 500 mg po/iv q24 Cefepime§2g iv q12h Piperacillin/tazobactam §3.375/4.5 g iv q6-8h Ertapenem 1g iv q24h Imipenem/cilastin§ 500 mg iv q 6 h **High risk of MRSA infection** †: Vancomycin 15mg/kg iv q12h Linezolid 600 mg po/iv q12h Daptomycin 4mg/kg iv q24h Telavancin 10mg/kg q24h Tigecycline 100 mg IV loading dose followed by 50 mg iv q12h Ceftaroline 600 mg iv q12h Cefepime§ 2g iv q12h plus vancomycin 15 mg/kg iv q12h Piperacillin/tazobactam §3.375/4.5g iv q6-8 h plus vancomycin 15mg/kg iv q12h Ertapenem 1g iv q24h plus vancomycin 15 mg/kg iv q12h Imipenem/cilastin§ 500 mg iv q 6 h plus vancomycin 15 mg/kg iv q12h
Acute osteomyelitis IDSA classification: Moderate*	Acute bone pain, swelling of affected site, drainage, fever, leukocytosis, and elevated CRP/ESR, and commonly with concomitant soft tissue involvement.	**No risk of MRSA infection:** Cefazolin 1-2 g iv q8h Ceftriaxone 1-2 g iv q24h Moxifloxacin 400 mg po/iv q24 Levofloxacin 500 mg po/iv q24 Cefepime§2g iv q12h Piperacillin/tazobactam §3.375/4.5 g iv q6-8h Ertapenem 1g iv q24h Imipenem/cilastin§ 500 mg iv q 6 **High risk of MRSA infection** †: Vancomycin 15 mg/kg iv q12h Linezolid 600 mg po/iv q12h Daptomycin 4 mg/kg iv q24h Telavancin 10 mg/kg q24h Tigecycline 100 mg IV loading dose followed by 50 mg iv q12 h Ceftaroline 600 mg iv q12h Ceftriaxone 1-2g iv q24h plus vancomycin 15mg/kg iv q12h Cefepime§ 2g iv q12h plus vancomycin 15mg/kg iv q12h Piperacillin/tazobactam §3.375/4.5g iv q6-8 h plus vancomycin 15mg/kg iv q12h Ertapenem 1g iv q24h plus vancomycin 15 mg/kg iv q12h Imipenem/cilastin§ 500 mg iv q 6 h plus vancomycin 15mg/kg iv q12h
Chronic osteomyelitis IDSA classification: Moderate*	Nonhealing large or deep ulcer, visible bone, positive probe-to-bone (PTB) test (palpable hard, gritty bone), or sinus tract overlying a bone structure, elevated ESR (>60 mm/hour), elevated CRP (>3.2 mg/dL). Fever and erythema are usually absent unless there is concomitant soft tissue infection	**No risk of MRSA infection:** Cefazolin 1-2 g iv q8h Ceftriaxone 1-2 g iv q24h Cefepime§2g iv q12h Piperacillin/tazobactam §3.375/4.5 g iv q6-8h Ertapenem 1g iv q24h Imipenem/cilastin§ 500 mg iv q 6 **High risk of MRSA infection** †: Vancomycin 15 mg/kg iv q12h Linezolid 600 mg po/iv q12h Daptomycin 4mg/kg iv q24h Telavancin 10mg/kg q24h Tigecycline 100 mg IV loading dose followed by 50 mg iv q12h Ceftaroline 600 mg iv q12h Ceftriaxone 1-2 g iv q24h plus vancomycin 15 mg/kg iv q12h Cefepime§ 2 g iv q12h plus vancomycin 15 mg/kg iv q12 h Piperacillin/tazobactam §3.375/4.5 g iv q6-8 h plus vancomycin 15 mg/kg iv q12 h Ertapenem 1 g iv q24h plus vancomycin 15 mg/kg iv q12h Imipenem/cilastin§ 500 mg iv q 6 h plus vancomycin 15 mg/kg iv q12h Ceftaroline 600 mg iv q12h plus metronidazole 500 mg iv q 8-12h

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate, q: every; h: hours; po: orally; iv: intravenously; MRSA: Methicillin-resistant S. aureus;
* Moderate infections with systemic toxicity or metabolic instability are considered severe infections according to IDSA classification.
† Previous/recent MRSA infection or colonization, communities with high MRSA prevalence, recent/prolonged hospitalization ,recent antibiotic use, hemodialysis, recent surgery, residence in a long term care facility, contact sports, military service, injection drug use, and men who have sex with men.
§ These antibiotics have activity against *pseudomonas* spp.

Table 1: Empiric treatment options of diabetic foot infections.

Conclusion

Proper utilization of antimicrobials is important for all wound care professionals. Wound care professionals have a unique position to lessen the inappropriate use of antimicrobials.

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Antibiotic	Antimicrobial activity	Clinical use and laboratory monitoring	Adverse effects
Amoxicillin/clavulanate (iv/po) *	Gram-positive organisms (such as MSSA, streptococcus species, and enterococci species), gram negative organisms (Enterobacteriaceae such as proteus mirabilis, E. coli, and Klebsiella species), and anaerobic organisms.	- Mild polymicrobial infections - A step down from parenteral antibiotic for moderate to severe infections. -Dose adjustment for renal dysfunction	Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and Abdominal pain, and rash
Ampicillin/sulbactam (iv) *	Gram-positive organisms, gram negative organisms and anaerobic organisms.	-Moderate to severe infections with/without antibiotic with anti-MRSA activity Dosage adjustment for renal dysfunction	Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and Abdominal pain, and rash
Piperacillin/tazobactam (iv) *	Active against gram-positive organisms, gram negative and anaerobic organisms.	-Moderate to severe infections with/without antibiotic with anti-MRSA activity - Dosage adjustment for renal dysfunction.	Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and Abdominal pain, and rash
Cephalexin (po) *	Active against gram-positive organisms and gram negative organisms	-Mild infections - Dose adjustment y for renal dysfunction.	Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and Abdominal pain, and rash
Ceftriaxone (iv) *	Active against gram-positive organisms and gram negative organisms	- Moderate to severe infections with/without antibiotic with anti-MRSA activity. - Good option for OPAT. - No dosage adjustment is necessary for renal dysfunction.	Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and Abdominal pain, increased liver enzymes, and rash.
Ceftazidime (IV) *	Active against gram-positive organisms, gram negative organisms	-Moderate to severe infections with antibiotic that has excellent activity against MSSA and with/without antibiotic with anti-MRSA activity -Dosage adjustment is necessary for renal dysfunction.	Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and Abdominal pain, and rash
Moxifloxacin(po or iv)	Active against gram-positive organisms, gram negative organisms and anaerobes	-Mild and moderate infections including osteomyelitis. - It is preferable to combine it with rifampin for the treatment of staphylococcal osteomyelitis - No dosage adjustment is necessary for renal dysfunction	Nausea, vomiting, diarrhea, headache, QT prolongation, tendon rupture, neurologic abnormalities, and CDI.
Ciprofloxacin (po or IV)	Active against gram-positive organisms (such as MSSA, and streptococcus species) and gram negative organisms (Enterobacteriaceae such as proteus mirabilis, E. coli, and Klebsiella spp., pseudomonas species, ESBL-producing organisms, and enterobacter spp,)	- Mild infections due to gram-negative organisms -Moderate infection in addition to antibiotic that has excellent activity against MSSA and with/without antibiotic with anti-MRSA activity - It is preferable to combine it with rifampin for the treatment of staphylococcal osteomyelitis - Dosage adjustment is necessary for renal dysfunction	Nausea, vomiting, diarrhea, headache, QT prolongation, tendon rupture, neurologic abnormalities, and CDI.
Levofloxacin (iv or po)	Active against gram-positive organisms (such as MSSA, and streptococcus species) and gram negative organisms (Enterobacteriaceae such as proteus mirabilis, E. coli, and Klebsiella species and pseudomonas spp.)	-Mild and moderate infections including osteomyelitis. -It is preferable to combine it with rifampin for the treatment of staphylococcal osteomyelitis -Dosage adjustment is necessary for renal dysfunction	Nausea, vomiting, diarrhea, headache, QT prolongation, tendon rupture, neurologic abnormalities, and CDI.
Clindamycin (po or iv)	Active against gram-positive organisms (MSSA, MRSA, and streptococcus species) and anaerobes (clostridium spp., peptostreptococcus spp.)	- Mild infections due to susceptible MRSA. - Mild infections due to MSSA and streptococci in patients with severe allergic reaction to β-lactams. - Moderate to severe infections as part of combination therapy. - No dosage adjustment is necessary for renal dysfunction.	Nausea, vomiting, diarrhea, and CDI.
Metronidazole (po or iv)	Active against anaerobic bacteria (bacteroides fragilis, clostridium spp., prevotella spp, porphyromonas spp)	- Moderate infection as part of combination antibiotic therapy. -Dosage adjustment is necessary for renal dysfunction.	Nausea, vomiting, disulfiram like reaction, and neuropathy.
Imipenem/cilastatin (IV)	Active against gram-positive organisms (such as MSSA, streptococcus species, and enterococci species), gram negative organisms (Enterobacteriaceae such as proteus mirabilis, E. coli, Klebsiella species, ESBL-producing organisms, enterobacter spp, acinetobacter species, and pseudomonas species), and anaerobic organisms.	- Moderate to severe infections with/without antibiotic with anti-MRSA activity -Dosage adjustment is necessary for renal dysfunction.	Diarrhea, nausea, vomiting, rash, seizure.
Ertapenem (iv)	Active against gram-positive organisms (such as MSSA, streptococcus species, and enterococci species), gram negative organisms (Enterobacteriaceae such as proteus mirabilis, E. coli, Klebsiella species, ESBLs-producing organisms, and enterobacter spp), and anaerobic organisms.	- Moderate to severe infections with/without antibiotic with anti-MRSA activity. -Good option for OPAT. -Dosage adjustment is necessary for renal dysfunction.	Diarrhea, nausea, vomiting, rash, seizure.

Vancomycin(IV)	Active against gram-positive organisms (such as MSSA, MRSA, streptococci spp, and, enterococci spp.) and gram positive anaerobic organisms (clostridium spp. And peptostreptococcus spp.)	-Moderate infections either alone or as part of combination infection when MRSA is a consideration or in patients with severe allergic reaction to β-lactams. - Severe infection as part of combination therapy when MRSA is a consideration or in patients with severe allergic reaction to β-lactams. - Dosage adjustment is necessary for renal dysfunction.	Infusion-related reaction, red man/ neck syndrome, nausea, vomiting, neutropenia, nephrotoxicity, and ototoxicity.
Linezolid (po or iv)	Active against gram-positive organisms (such as MSSA, MRSA, VISA, VRSA, streptococci spp, and, enterococci spp. Including VRE) and gram positive anaerobic organisms (clostridium spp. And peptostreptococcus spp.)	- Moderate infection either as monotherapy or part of combination therapy when vancomycin cannot be used. - Severe infection as part of combination therapy when vancomycin cannot be used. - No dosage adjustment is necessary for renal dysfunction.	Diarrhea, nausea, headache, myelosuppression, optic neuritis, peripheral neuropathy, lactic acidosis, serotonin syndrome, and DRESS (drug rash and eosinophilic systemic symptoms syndrome with acute interstitial nephritis.).
Daptomycin (iv)	Active against gram-positive organisms (such as MSSA, MRSA, VISA, VRSA, streptococci spp, and, enterococci spp. Including VRE)	- Moderate infection either as monotherapy or part of combination therapy when vancomycin cannot be used. - Severe infection as part of combination therapy when vancomycin cannot be used. - Good option for OPAT. - Dosage adjustment is necessary for renal dysfunction.	GI side effects, headache, myopathy, elevated creatinine kinase (CK), rarely rhabdomyolysis, eosinophilic pneumonitis, and hepatotoxicity.
Tigecycline (iv)	Active against gram-positive organisms (such as MSSA, MRSA, VISA, VRSA, streptococcus species, and enterococci species including VRE), gram negative organisms (Enterobacteriaceae such as E. coli, Klebsiella species, ESBLs-producing organisms, and enterobacter spp, and acinetobacter), and anaerobic organisms.	- Moderate and severe polymicrobial infections. - It should not be used in severe infection with concomitant bacteremia due to its very low serum concentrations - No dosage adjustment is necessary for renal dysfunction but required for severe hepatic dysfunction.	Nausea, vomiting, increased liver function tests, and permanent staining of developing teeth.

MSSA: Methicillin-Sensitive *Staphylococcus aureus*; MRSA: Methicillin-Resistant *Staphylococcus aureus;* VRE: Vancomycin Resistant Enterococci; ESBLs: Extended Spectrum β-Lactamases; CDI: Clostridium Difficile Infection; VISA: Vancomycin Intermediate *Staphylococcus aureus*; VRSA: Vancomycin Resistant *Staphylococcus aureus*; OPAT: Outpatient Parenteral Antibiotic Therapy.
*All penicillins and cephalosporines can cause hypersensitivity reaction, cytopenia, interstitial nephritis, hemolytic anemia, hepatotoxicity, pseudomembranous colitis, serum sickness-like reaction, vaginitis, and seizure with high doses and/or renal failure.

Table 2: Commonly used antibiotics for the treatment of diabetic foot infections in clinical trials.

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