

# Update on the Antimicrobial Management of Foot Infections in Patients With Diabetes

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Selecting appropriate antibiotics for the treatment of diabetic foot infections (DFIs) is crucial. Identifying the optimal antibiotic choice requires careful consideration of three major criteria: severity of infection, duration of wounds, and previous antibiotic exposure.

Chronic wounds can be colonized on the surface by a varied group of organisms, including aerobic gram-positive cocci (e.g., staphylococci, streptococci, and enterococci), enterobacteriaceae (e.g., *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and *Proteus* spp.), nonfermentive gram-negative rods (e.g., *Pseudomonas aeruginosa*), and anaerobic bacteria. Isolates from superficial swab cultures may not represent the underlying infecting pathogen.<sup>1</sup> Therefore, cultures obtained after the debridement of superficial debris, eschar, or calluses are best to guide targeted antibiotic therapy.<sup>2</sup> Once the probable pathogen(s) are isolated, de-escalation of empiric therapy can be guided by relevant culture results.

The severity of infection affects several treatment decisions. These include the route and choice of antibiotic, the need for hospital admission, consideration of surgical intervention, and overall length of therapy.

DFIs are characterized by the presence of at least two of the following clinical symptoms: localized edema, erythema, pain, and purulent discharge. Mild infections

involve only the skin or subcutaneous tissue, and erythema, if present, is within 2 cm of an ulcer. Most mild infections and many moderate infections can be treated by narrow-spectrum antibiotics focused against staphylococcal and streptococcal bacteria.<sup>3</sup> Suggested treatment of mild DFIs consists of oral agents with activity against *Staphylococcus aureus* (Table 1).

Moderate infections refer to those with surrounding erythema > 2 cm or deeper infections that extend beyond the subcutaneous structures (e.g., deep abscesses, septic arthritis, or osteomyelitis). Severe infections are defined as cases with both local signs of infection and a systemic inflammatory response (e.g., leu-

kocytosis, fever, hypotension, or tachycardia). Empiric treatment for moderate to severe DFIs includes an expansive assortment of options (Table 2).

The differing pharmacological properties of these agents must be thoughtfully considered when selecting antimicrobial therapy. For infections of greater severity, empiric therapy usually includes activity against both aerobic gram-positive and gram-negative organisms. Longstanding infections or infections with necrotic tissue often harbor anaerobic bacteria in addition to those listed above. Generally, these infections require the use of broad-spectrum antibiotics with additional activity against anaerobes such as *Bacteroides fragilis*.

Patient-specific factors also influence optimal antibiotic choice. Patients with diabetes are at a high risk of compromised skin integrity and impaired wound healing because of complications such as peripheral neuropathy, vascular insufficiency, and hyperglycemia.

DFIs without open skin wounds or with ulcers of limited duration are typically caused by gram-positive organisms, including *S. aureus* and  $\beta$ -hemolytic streptococci (Groups A, B, C, and G). In a study of 653 post-debridement samples from diabetic foot wounds,<sup>4</sup> aerobic gram-positive organisms accounted for 77% of all bacterial isolates, with staphylococci (43%) and streptococci (13%) representing the largest proportion

## IN BRIEF

Foot infections are common problems in patients with diabetes and can lead to devastating complications and long-term morbidity. Although these infections invariably start in superficial soft tissues, they can involve deeper structures, including bone. Complications may include necrotizing fasciitis, soft tissue gangrene, septic arthritis, and osteomyelitis. This article reviews the factors involved in appropriate antibiotic selection and describes antimicrobial agents included in recently updated treatment guidelines from the Infectious Diseases Society of America.

**Table 1. Spectrum of Activity of Suggested Oral Antibiotics for the Treatment of Mild DFIs**

	Activity Against MSSA	Activity Against MRSA	Activity Against Enterobacteriaceae
Dicloxacillin	Yes	No	No
Clindamycin	Yes	Yes for community-acquired strains, inducible resistance reported (detected by D-test)	No
Cephalexin	Yes	No	Limited, but covers some strains of <i>E. coli</i>
Amoxicillin-clavulanate	Yes	No	Yes, but high rates of <i>E. coli</i> resistance
Minocycline	Yes	Yes	Limited
Trimethoprim-sulfamethoxazole	Yes	Yes	Limited
Levofloxacin	Only variable activity against MSSA	No	Yes, broad-spectrum activity

*MRSA, methicillin-resistant S. aureus; MSSA, methicillin-sensitive S. aureus*

of these organisms. Wounds of < 6 weeks' duration coincided with the greatest number of gram-positive infections. In contrast, gram-negative infections were more prevalent in patients with wounds present for ≥ 6 weeks.

The inclusion of anti-pseudomonal spectrum in the treatment of DFIs is common but controversial. Empiric antibiotic therapy with activity against *P. aeruginosa* (i.e., ceftazidime, cefepime, piperacillin-tazobactam, imipenem, or meropenem) is advised for patients with risk factors for this organism, those who have undergone recently failed nonpseudomonal therapy, and in cases of severe infection. Risk factors for *P. aeruginosa* infection include warm climate, open wounds that have been soaked in water, and a high local rate of pseudomonal infections.<sup>3</sup>

Surprisingly, clinical improvement in severe infections has been observed with regimens devoid of meaningful *P. aeruginosa* activity regardless of microbiological culture

results.<sup>5-7</sup> For example, clinical response did not differ in a study that compared ertapenem, an agent lacking anti-pseudomonal activity, to piperacillin-tazobactam in 586 patients with moderate to severe DFIs.<sup>5</sup> Some caution is advised in interpreting this finding because only 28 cultures in this study isolated *P. aeruginosa*.

Patients with DFIs have numerous hospitalizations and are often exposed to multiple courses of antibiotics.<sup>8</sup> Previous antibiotic exposure can have a substantial influence on anticipated antimicrobial resistance. Kaye et al.<sup>9</sup> reported that patients with previous treatment with penicillin-based therapy had higher rates of *E. coli* resistance to the β-lactam/β-lactamase inhibitor combination ampicillin-sulbactam. Fluoroquinolone use has been associated with an increase in the acquisition of methicillin-resistant *S. aureus* (MRSA).<sup>10,11</sup> A common risk factor for the development of highly resistant bacteria is the previous use of broad-spectrum antimicro-

bials.<sup>12,13</sup> To minimize antibiotic exposure, chronic wounds without clinical signs of infection should not be cultured.<sup>3</sup> Unwarranted microbiological samples may encourage the use of antibiotic therapy and thereby increase the risk of harboring multi-drug-resistant organisms.

**Expanded-Spectrum Penicillin-Based Therapy**

Expanded-spectrum penicillin-based regimens include dicloxacillin and β-lactam/β-lactamase inhibitor combinations. Dicloxacillin, an oral penicillinase-resistant penicillin, is a recommended treatment for mild DFIs. This agent has excellent activity against methicillin-sensitive *S. aureus* (MSSA) and β-hemolytic streptococci but has no activity against gram-negative pathogens. Although inexpensive, dicloxacillin has variable oral absorption and requires dosing four times daily.

Other penicillin-based therapies consist of β-lactam/β-lactamase inhibitor combinations such as amoxicillin-clavulanate, ampicillin-

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**Table 2. Characteristics of Suggested Antibiotic Regimens for Moderate to Severe DFIs**

	Available formulations	Once-Daily Dosing	Activity Against MRSA	Activity Against <i>P. aeruginosa</i>	Activity Against <i>B. fragilis</i>
Ampicillin-sulbactam	IV	No	No	No	Yes
Levofloxacin	IV and oral	Yes	No	Variable resistance rates	No
Ciprofloxacin plus clindamycin	IV and oral	No	Yes for clindamycin, but variable resistance rates	Yes for ciprofloxacin, but variable resistance rates	Yes for clindamycin, but variable resistance rates
Moxifloxacin	IV and oral	Yes	No	No	Yes, but rare resistance
Cefoxitin	IV	No	No	No	Yes, but some resistance
Ceftriaxone	IV	Yes	No	No	No
Ertapenem	IV	Yes	No	No	Yes
Piperacillin-tazobactam	IV	No	No	Yes	Yes
Imipenem	IV	No	No	Yes	Yes
Linezolid	IV and oral	No	Yes	No	No
Daptomycin	IV	Yes	Yes	No	No

*IV, intravenous; MRSA, methicillin-resistant S. aureus*

subactam, ticarcillin-clavulanate, and piperacillin-tazobactam. The addition of a β-lactamase inhibitor increases the spectrum of penicillin-based antibiotics to include MSSA, certain β-lactamase-producing gram-negatives, and anaerobes such as *B. fragilis*. Amoxicillin-clavulanate and ampicillin-sulbactam are almost identical with regard to spectrum, with activity against gram-positive organisms, enterobacteriaceae, and obligate anaerobes. Of note, isolates of *E. coli* can be resistant to these agents, particularly in patients with previous antibiotic exposure.<sup>9</sup> A recent study of *E. coli* bloodstream infections<sup>14</sup> observed an increase in ampicillin-sulbactam resistance over a 10-year period.

Piperacillin-tazobactam is a parenteral ureidopenicillin/β-lactamase

inhibitor combination with broad-spectrum coverage of aerobic gram-positives, obligate anaerobes, and aerobic gram-negatives. In comparison to ampicillin-sulbactam, piperacillin-tazobactam has similar activity against gram-positive and anaerobic bacteria but has an increased spectrum against non-fermentive gram-negative rods including *P. aeruginosa*. This difference in gram-negative activity may not translate into a clinical advantage for all cases of DFIs. An open-label, randomized study<sup>15</sup> compared these two agents in 314 adult patients with moderate to severe infections of diabetic foot ulcers. The clinical efficacy rate for ampicillin-sulbactam was found to be statistically equivalent to piperacillin-tazobactam (83.1 vs. 81%,

respectively). Although ticarcillin-clavulanate has been studied in the treatment of DFIs, it has mainly been supplanted by piperacillin-tazobactam and is infrequently used.

**Cephalosporins**

Cephalosporins are semisynthetic β-lactams classified by generations. Generally, cephalosporins in higher generations have enhanced activity against gram-negative organisms but have varying degrees of activity against gram-positive cocci.

The spectrum of first-generation cephalosporins is focused against gram-positive bacteria. Cephalexin is an oral first-generation cephalosporin with activity against MSSA, streptococcus spp., and some strains of enteric gram-negative bacilli such as *E. coli*. This agent has been

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studied in the treatment of uncomplicated lower-extremity infections in diabetic patients.<sup>16</sup> Cephalexin usually requires dosing four times daily but offers a cost-effective option for mild DFIs.

Cefoxitin is a parenteral second-generation cephalosporin with activity against gram-positive, gram-negative, and anaerobic bacteria. This antimicrobial is usually given every 6 hours and, although active against obligate anaerobes, an increasing rate of *B. fragilis* resistance has been observed.<sup>17</sup>

Ceftriaxone is an injectable third-generation cephalosporin that provides broad-spectrum gram-positive and gram-negative activity. Ceftriaxone lacks clinically useful activity against bacteroides spp. and should be combined with an agent such as metronidazole if anaerobic pathogens are also suspected.<sup>18</sup> An open-label study<sup>19</sup> compared metronidazole plus ceftriaxone to ticarcillin/clavulanate as empiric treatment for diabetic lower-extremity infections in older men. Both regimens had similar treatment success rates (72 and 76%, respectively). Convenient once-daily dosing makes ceftriaxone an attractive parenteral option for outpatient therapy.

### Carbapenems

Carbapenems are broad-spectrum parenteral antimicrobials that have activity against gram-positive, gram-negative, and anaerobic bacteria. Carbapenems should be reserved for treatment of infections likely to be caused by multi-antibiotic-resistant gram-negatives (e.g., when extended-spectrum  $\beta$ -lactamase [ESBL]-producing organisms are of particular concern). Both imipenem and meropenem have been studied for the treatment of diabetic foot infections in subsets of patients with complicated skin and skin structure infections.<sup>20</sup> The three available

carbapenems—imipenem, meropenem, and doripenem—have similar spectrums of activity that include ESBL-producing gram-negatives and *P. aeruginosa*.

Although also parenterally administered, ertapenem is the only carbapenem with once-daily dosing. With regard to therapeutic spectrum, ertapenem lacks clinical activity against enterococcus spp. and *P. aeruginosa*.<sup>21</sup> A difference in clinical outcomes was not observed in trials<sup>5,22</sup> comparing piperacillin-tazobactam to carbapenem-based therapy.

Carbapenem use has been associated with the emergence of multi-drug-resistant *P. aeruginosa* and *K. pneumonia*. Therefore, these antimicrobials must be used judiciously.<sup>23–25</sup> Involvement of an infectious diseases specialist should be considered for patients who require the use of these agents.

### Fluoroquinolones

Ciprofloxacin, levofloxacin, and moxifloxacin are potential options for the empiric treatment of DFIs.<sup>3</sup> These fluoroquinolones are available in both oral and intravenous formulations, but differ with regard to antibacterial spectrum. Ciprofloxacin should be used in combination with clindamycin because of its relatively poor gram-positive activity. In contrast to ciprofloxacin, levofloxacin has improved gram-positive activity but is less potent against *P. aeruginosa*. Moxifloxacin possesses activity against obligate anaerobes, including *B. fragilis*, but lacks clinical utility for pseudomonal infections. Although levofloxacin and moxifloxacin can be used as empiric monotherapies, they may not provide reliable activity against *S. aureus*, particularly when MRSA is suspected.<sup>26</sup>

Most of the published fluoroquinolone DFI data have been derived from smaller subsets of patients

within larger studies of skin and skin structure infections. Graham et al.<sup>27</sup> compared levofloxacin in the treatment of complicated soft tissue infections to ticarcillin-clavulanate followed by oral amoxicillin-clavulanate. For the subset of 54 patients with DFIs, a clinical success rate of 69.2% for levofloxacin and 57.1% for ticarcillin-clavulanate/amoxicillin-clavulanate was observed. In two trials,<sup>6,7</sup> moxifloxacin monotherapy was shown to be clinically non-inferior to a regimen consisting of initial piperacillin-tazobactam therapy with a sequential switch to oral amoxicillin-clavulanate. Both studies included patients with DFIs, but these were smaller subsets within larger groups with skin and skin structure infections. For example, one study using moxifloxacin<sup>6</sup> included only 78 DFIs from among 617 patients enrolled in the original study. Because it has no demonstrated clinical superiority over other well-established treatment choices, empiric fluoroquinolone therapy should be reserved for  $\beta$ -lactam-allergic patients.

### Agents Active Against MRSA

The prevalence of MRSA in DFIs has increased compared to historic rates and has been reported to be as high as 30%.<sup>28</sup> Risk factors for MRSA isolation from DFIs include chronic ulcers of > 6 weeks' duration, previous hospitalization, long-term antibiotic use, osteomyelitis, previous history of MRSA infection, and MRSA nasal colonization.<sup>4,28–30</sup> Empiric coverage of MRSA should be considered for patients with previous isolation of MRSA within the past year, high local MRSA rates (prevalence rates of 50% for mild infections and 30% for moderate infections), or severe infections while awaiting definitive culture results.<sup>3</sup>

For mild infections, oral agents with MRSA activity include

minocycline, trimethoprim-sulfamethoxazole (TMP-SMX), and clindamycin. Although TMP-SMX and minocycline have in vitro activity against many isolates of MRSA, their activity against streptococcal species is not uniform. For example, group B streptococci are intrinsically resistant to TMP-SMX, and tetracycline-resistant group A streptococci are widely prevalent. An additional agent such as amoxicillin should be added if  $\beta$ -hemolytic streptococci coverage is required.<sup>30</sup>

Clindamycin, a lincosamide, is available in both intravenous and oral formulations. This agent has activity against community acquired strains of MRSA,  $\beta$ -hemolytic streptococci, and anaerobic bacteria. However, MRSA isolates should be tested for inducible clindamycin resistance because treatment failures have been reported.<sup>31</sup>

Treatment options for moderate to severe DFIs with MRSA include vancomycin, daptomycin, and linezolid. Vancomycin, a glycopeptide antimicrobial, has been the traditional agent used to cover MRSA in more severe DFIs. Optimal dosing is important because patients with diabetes may have reduced penetration of vancomycin into soft tissue compared to patients without diabetes.<sup>32</sup> Additionally, some strains of *S. aureus*, compared to historic isolates, have shown a decreasing sensitivity to vancomycin.

The consensus recommendations published in 2009<sup>33</sup> offer guidance regarding the suggested dosing and monitoring for complicated MRSA infections. In the setting of vancomycin hypersensitivity or clinical failure, alternatives such as daptomycin or linezolid could be considered.

Linezolid, an oxazolidinone, has been studied in complicated skin and skin structure infections including DFIs. A pooled review<sup>34</sup> of 349

patients with diabetes receiving either linezolid or vancomycin for complicated skin and skin structure infections observed comparable rates of clinical success (74 and 71%, respectively). Linezolid is available in both intravenous and oral formulations and is active against aerobic gram-positive organisms, including MRSA and vancomycin-resistant enterococcus. This agent is well absorbed orally but considerably more expensive than the older oral antibiotics previously mentioned. Because of frequent myelosuppression, complete blood counts should be monitored for treatment courses > 14 days. One study<sup>35</sup> reported anemia (17.6%), thrombocytopenia (12.8%), and neutropenia (2.0%) associated with linezolid use. Furthermore, linezolid interacts with medications that increase concentrations of serotonin, resulting in rare but sometimes severe cases of serotonin syndrome.<sup>36</sup>

Daptomycin is a parenteral cyclic lipopeptide similar in spectrum to vancomycin with activity against gram-positive organisms. Once-daily dosing makes this an attractive outpatient option, but serial monitoring of creatine phosphokinase is recommended because of potential myopathy.<sup>37</sup> In a subset of 103 patients with DFIs, daptomycin had similar outcomes to either vancomycin or penicillinase-resistant semisynthetic penicillin (66 and 70%, respectively).<sup>38</sup>

Tigecycline is a parenteral broad-spectrum glycycline antibiotic. Although active against MRSA, this agent has been found to be inferior to other antimicrobials in the treatment of DFIs.<sup>39</sup>

Mild DFIs involving MRSA can be treated with inexpensive oral options such as TMP-SMX, minocycline, or clindamycin. Vancomycin is still an appropriate choice for MRSA coverage in moderate to severe DFIs.

The superiority of alternative agents such as linezolid or daptomycin in the treatment of DFIs has not been demonstrated.

### Conclusion

Identifying the appropriate antimicrobial treatment of DFIs is a complex process with many patient-specific considerations. Proper selection of antimicrobial therapy is imperative but often difficult because of polymicrobial colonization of chronic diabetic ulcers. Therapy must have activity against gram-positive organisms and, if risk factors are present, include coverage of MRSA. The role of *P. aeruginosa* therapy is less clear, and empiric antimicrobial coverage is not always necessary for this organism.

Regimens studied have not demonstrated meaningful superiority of any particular agent. The majority of published data pertain to the use of  $\beta$ -lactam-based regimens. Newer agents such as ertapenem and moxifloxacin are possible choices in the treatment of DFIs but should be considered only as alternative agents. Although linezolid and daptomycin are other potential treatment options for MRSA, no compelling evidence indicates the need to replace vancomycin for the treatment of DFIs. Linezolid and daptomycin generally should be reserved for cases of vancomycin failure or hypersensitivity.

The optimal antimicrobial treatment of DFIs has yet to be determined. Additional prospective, well-designed trials are needed to clarify which regimen(s) result in the best possible outcomes.

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