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REVIEW

The Role of Novel Antibiotics in the Management of Diabetic Foot Infection

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ABSTRACT

Diabetic foot infection is a frequent and potentially life-threatening complication of diabetes mellitus. Antibiotic treatment is the cornerstone of management of diabetic foot infection but the rising prevalence of antibiotic resistance has resulted in increasing rates of treatment failure. In this context, the development of several novel antibiotics might represent a useful tool in severe diabetic foot infections caused by multidrug-resistant bacteria. In the present review, we summarize the safety and efficacy of novel antibiotics in patients with diabetic foot infection. Relevant data are limited, and randomized controlled studies that evaluated the role of these agents in this field are lacking. Until more robust data are available, cefiderocol and dalbavancin, which have been studied more extensively in patients with bone infections, might be attractive options in carefully selected patients with severe diabetic foot infection.

Keywords: Diabetes mellitus; Diabetic foot infection; Antibiotics; Dalbavancin; Oritavancin; Tedizolid; Ceftaroline; Ceftazidime/avibactam; Meropenem/vaborbactam; Imipenem-cilastatin/relebactam; Ceftolozane/azobactam; Plazomicin; Cefiderocol

Key Summary Points

The selection of the appropriate antibiotic in patients with diabetic foot infection is complicated by the rising prevalence of multidrug-resistant bacteria.

Among novel antibiotics, cefiderocol and dalbavancin might be attractive options in carefully selected patients with severe diabetic foot infection.

Collections of appropriate specimens to identify the causative pathogen(s) is a sine qua non for the successful treatment of diabetic foot infection.

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INTRODUCTION

Diabetic foot infection is a leading cause of non-traumatic lower limb amputation [1]. It is also associated with increased risk for cardiovascular and all-cause mortality in patients with diabetes mellitus [2]. According to current guidelines, the management of severe diabetic foot infection consists of assessment for need for surgical treatment, evaluation for peripheral arterial disease and urgent management if present and administration of empiric broad-spectrum antibiotic treatment targeting both gram-positive and -negative bacteria, including anaerobes [3]. The antibiotic therapy should then be adjusted based on both the clinical response and culture findings [3]. The most common pathogens causing diabetic foot infection are *Staphylococcus aureus, Pseudomonas aeruginosa* and *Escherichia coli*, whereas almost one fifth of cases are polymicrobial [4, 5]. However, the presence of antibiotic-resistant pathogens is becoming more frequent in diabetic foot infection [6–8]. Indeed, almost 20% of bacteria causing diabetic foot infection are multidrug resistant, particularly *S. aureus* and *P. aeruginosa* [4, 9]. Accordingly, the incidence of failure of antibiotic treatment is also rising [10]. Overuse of broad-spectrum antibiotics is a major cause of the emergence of resistant bacteria [11]. An earlier meta-analysis did not identify clear differences in resolution of diabetic foot infection among conventional carbapenems, antipseudomonal penicillins and cephalosporins [12]. In this context, recently approved antibiotics might have a role in the management of difficult-to-treat diabetic foot infections.

In the present review, we summarize the role of novel antibiotics in the management of these patients. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CEPHALOSPORINS

Ceftaroline

Ceftaroline is a fifth-generation cephalosporin and is approved for the treatment of acute bacterial skin and skin-structure infections (ABSSSI) (with additional approval for *S. aureus* bacteremia associated with ABSSSI) and community-acquired pneumonia [13]. Ceftaroline exhibits activity against methicillin-resistant *S. aureus* (MRSA) through binding penicillin-binding protein 2a (PBP2a), but also against many gram-positive and -negative pathogens [*Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, coagulase-negative *Staphylococcus* (CoNS), *Klebsiella spp, E. coli*], with the exception of non-fermentative (*P. aeruginosa, Acinetobacter baumannii*) and multidrug-resistant gram-negative bacilli [extended spectrum β-lactamase (ESBL) or *Klebsiella pneumoniae* carbapenemase (KPC) producing isolates] [13–15]. Ceftaroline is used at a standard intravenous dose of 600 mg every 12 h if creatinine clearance is $>$ 50 ml/min and the dose may be increased to 600 mg every 8 h in the case of complicated skin and soft tissue infections (SSTIs) caused by *S. aureus* with a minimal inhibitory concentration (MIC) 2 or 4 mg/l to ceftaroline [15]. Dosage adjustment is required for altered kidney function with creatinine clearance $\leq$ 50 ml/min. Ceftaroline is well tolerated, and its most common adverse reactions are gastrointestinal (diarrhea, nausea), headache, pruritus and *Clostridium difficile* infection, even though there are some post-market reports of myelotoxicity related to prolonged ($>$ 7 days) ceftaroline exposure [13–15].

Approval of ceftaroline was based on two clinical studies, CANVAS 1 and 2, which excluded patients with diabetic foot infection and therefore; the use of ceftaroline for treatment of diabetic foot infection is off-label [16]. However, increasing data support the potential role of ceftaroline for diabetic foot infection as monotherapy or in combination with other antibiotics for wider gram-negative and anaerobic coverage. Retrospective data from the Clinical Assessment Program and Teflaro®

Utilization Registry (CAPTURE) registry (n = 201 patients with diabetic foot infection) showed clinical success in 81% of patients who received ceftaroline for a mean duration of 6.1 days, either as monotherapy (65%) or in combination with other antibiotics [16]. Interestingly, the presence of comorbidities, the type of pathogen and the need for surgical intervention did not affect the outcome [14]. Of note, in the CAPTURE registry, there were higher MRSA isolation rates (28%) than in other studies [16]. In another retrospective cohort of 223 patients with diabetic foot infection, the use of ceftaroline was associated with lower 90-day hospital re-admission and mortality compared with daptomycin [17]. There are also data from the CAPTURE registry indicating clinical success with ceftaroline in gram-positive osteomyelitis in patients with diabetes [18]. In this registry, 150 patients with osteomyelitis (59.3% with diabetes or peripheral arterial disease) due to gram-positive bacteria received ceftaroline, and clinical success rates were very high and similar in the total population and in patients with diabetes (92.7 and 91.0%, respectively) as well as in those who received ceftaroline monotherapy or in combination with other antibiotics (91.0 and 96.0%, respectively) [18]. Moreover, only 1.3% of patients discontinued ceftaroline because of adverse effects [18].

Ceftazidime/Avibactam

The combination of ceftazidime, a third generation cephalosporin, and avibactam, a non-β-lactam inhibitor of β-lactamases, is effective against a spectrum of gram-positive cocci and gram-negative bacilli, including *P. aeruginosa*, KPC, ESBL and oxacillinase (OXA) 48, but not against *Acinetobacter* and Ambler class B metallo-β-lactamases (MBL), while it has poor activity against anaerobic bacteria [19]. It is approved for complicated urinary tract infections (cUTIs) and complicated intra-abdominal infections (cIAI) [20, 21]. Notably, case series suggest that ceftazidime/avibactam is effective in the treatment of bone and joint infection [22]. Moreover, current guidelines recommend the use of ceftazidime monotherapy for moderately severe or severe infections to cover gram-negative bacteria and *Pseudomonas* [23]. Therefore, ceftazidime/avibactam might have a role in the management of diabetic foot infection caused by carbapenem-resistant *Enterobacteriaceae* (CRE) and carbapenem-resistant *P. aeruginosa* [24]. However, ceftazidime/avibactam is affected by mechanisms of resistance such as efflux pumps and porin channel mutations that are commonly used by multidrug resistant (MDR) *Pseudomonas* and is less effective in vitro than ceftolozane/tazobactam against MDR *Pseudomonas* [20].

Ceftolozane-Tazobactam

Ceftolozane is a fifth-generation cephalosporin and is effective against *P. aeruginosa* [25]. Its combination with tazobactam was first approved in 2015 for the management of complicated cUTIs and cIAIs [20]. Ceftolozane/tazobactam is effective against gram-negative bacilli, including ESBL *Enterobacteriaceae* and MDR *P. aeruginosa*, but has minimal activity against gram-positive bacteria, particularly *Streptococcus* and *Enterococcus* species [20]. Therefore, ceftolozane/tazobactam might have a role in diabetic foot infection caused by MDR gram-negative bacteria [24, 25]. A case of a patient with diabetic foot infection due to MDR *P. aeruginosa* who was successfully managed with ceftolozane-tazobactam in combination with fosfomycin was recently reported [26].

Cefiderocol

Cefiderocol is a novel parenteral siderophore cephalosporin with unique mode of action, mediated through its catechol side chain [27]. By forming a chelated complex with ferric iron, cefiderocol enters the outer lipopolysaccharide membrane of gram-negative bacteria through the bacterial iron transport system. Like other cephalosporins, it binds to penicillin-binding proteins (PBPs) and inhibits bacterial cell wall synthesis [28].

Cefiderocol is resistant to hydrolysis by all classes of β-lactamases, including KPC, OXA and MBL [29, 30]. As a result, its antibacterial

spectrum includes resistant *Enterobacterales*, *P. aeruginosa*, *A. baumannii* and *Stenotrophomonas maltophilia*, while it has poor gram-positive and anaerobic activity [31–33]. The successful evasion of all carbapenem-resistance mechanisms renders cefiderocol a particularly attractive choice for the treatment of infections due to MBL-producing pathogens and *A. baumannii*, where antimicrobial options are limited.

The adverse effect profile of cefiderocol is comparatively favorable and similar to other β-lactams. The most frequently reported adverse events are diarrhea, rash, infusion site reactions, pyrexia and elevation in liver function tests [34]. In the CREDIBLE-CR study, rates of drug-related acute kidney injury were lower in the cefiderocol arm than in the best available therapy arm [35]. These results are appealing because alternative therapies for MBL-producing bacteria and extensively drug-resistant (XDR) *A. baumannii*, such as polymyxins and aminoglycosides, are associated with increased risk for nephrotoxicity.

To date, cefiderocol has been granted authorization for the treatment of cUTIs, hospital-acquired pneumonia (HAP) and ventilator-associated bacterial pneumonia (VAP) with limited or no alternative treatment options [26]. However, this agent has also been successfully employed for compassionate use in other indications [36, 37]. In the CREDIBLE-CR study, cefiderocol showed comparable clinical and microbiological efficacy with best available treatment in patients with nosocomial pneumonia, bloodstream infections or cUTIs caused by carbapenem-resistant gram-negative bacteria. However, cefiderocol carries a Food and Drug Administration label warning, in the light of CREDIBLE-CR results demonstrating an increased all-cause mortality in the cefiderocol arm compared with the best available therapy arm, with no clear cefiderocol-related toxicity or other explanation for this finding [26]. Interestingly, cefiderocol is the first novel antimicrobial agent that is expected to be approved for the treatment of infections caused by carbapenem-resistant *A. baumannii* [32].

Favorable experience with the use of cefiderocol in the treatment of osteomyelitis has been recently reported, potentially extending its utility in diabetic foot infections, where the incidence of multidrug-resistant pathogens is rising [6, 7]. Chavda et al. described the successful use of cefiderocol for the treatment of osteomyelitis due to a pan-resistant *P. aeruginosa*. More specifically, 28 days of cefiderocol treatment in combination with an oral fluoroquinolone, in combination with surgical debridement, resulted in clinical improvement and avoidance of amputation [38]. Alamarat et al. also reported the case of successful management of osteomyelitis caused by XDR *P. aeruginosa* and ESBL *K. pneumoniae* in a pediatric patient, with prolonged administration of cefiderocol [39]. Similarly, Dagher et al. efficiently treated a case of extensively drug-resistant *A. baumannii* osteomyelitis with cefiderocol in combination with surgical debridement, where alternative antimicrobial options did not exist [40].

Notably, iron is known to be utilized in the formation of biofilm, and siderophore production has been shown to be increased in biofilms. Thus, cefiderocol with its unique exploitation of the bacterial iron transport system might prove to be particularly efficacious against infections characterized by biofilm formation, such as in the case of bone infections [41, 42].

CARBAPENEMS

The combination of meropenem, a wide spectrum carbapenem, and vaborbactam, a boronic β-lactamase inhibitor of class A and C, such as KPC, ESBL and ampicillinase C (AmpC), is approved for the management of UTIs [20, 43]. However, meropenem/vaborbactam is not active against OXA-type carbapenemases and MBL (class B) or MDR *P. aeruginosa* and *Acinetobacter* [20]. This agent was shown to be as effective as piperacillin-tazobactam in the management of UTIs and as effective as the best available therapy in a variety of infections caused (or suspected to be caused) by CRE, including cUTIs, cIAI, HAP and VAP [21]. Therefore, meropenem/vaborbactam might be an option in diabetic foot infection caused by CRE producing KPC but has not been studied in these patients [24].

The combination of imipenem, a wide-spectrum carbapenem, with cilastatin, which delays the degradation of imipenem and prolongs its antibiotic effect, and with relebactam, a novel β-lactamase inhibitor that provides effectiveness against class A and C β-lactamases, but not class B, was shown to be more effective than imipenem/cilastatin in patients with cUTIs and cIAIs [20, 21]. This agent is also effective against carbapenemase-resistant *P. aeruginosa* and might be a suitable option for the treatment of diabetic foot infection caused by this pathogen or by KPC-producing CRE, even though relevant studies are lacking [24].

AMINOGLYCOSIDES

Plazomicin is a next-generation aminoglycoside that displays dose-dependent bactericidal activity against *Enterobacteriaceae* including strains that produce ESBL as well as some carbapenemases such as KPC and OXA-48 [44–47]. However, it lacks activity against many New Delhi metallo-β-lactamase (NDM)-harboring strains, its activity toward *P. aeruginosa* and *A. baumannii* is variable and similar to other aminoglycosides, and it is not active against anaerobes [48–50]. Interestingly, plazomicin shows activity against *S. aureus* and CoNS, including methicillin-resistant strains [49], which are frequently encountered in polymicrobial diabetic foot infections. Plazomicin is labeled for the treatment of cUTI, including pyelonephritis, and is reserved for patients with limited or no alternative treatment options [44]. Its main side effects are nephrotoxicity and ototoxicity, similar to other members of this class of antibiotics [44].

In the EPIC trial, plazomicin demonstrated non-inferiority compared to meropenem in composite clinical and microbiological cure at the test-of-cure visit in patients with cUTI and acute pyelonephritis caused by *Enterobacteriaceae*, including MDR pathogens [51]. In the Combating Antibiotic-Resistant *Enterobacteriaceae* (CARE) trial, plazomicin-based were compared with colistin-based combinations in patients with CRE-related bloodstream infections, HAP and VAP. Unfortunately, the study was terminated prematurely because of difficulties in enrollment, but preliminary findings showed lower all-cause mortality and less serious adverse events, including nephrotoxicity, in the plazomicin arm [52].

To the best of our knowledge, there are no studies evaluating the use of plazomicin in the treatment of SSTIs and bone infections, including diabetic foot infections. However, pharmacokinetic studies demonstrated that aminoglycosides effectively penetrate into bone and joint tissues, despite their hydrophilicity [53]. Moreover, plazomicin was found to be active and superior, compared with the older aminoglycosides, against CRE isolates from SSTIs [54].

LIPOGLYCOPEPTIDES

Dalbavancin

Dalbavancin is a novel long-acting lipoglycopeptide and is active against gram-positive pathogens, including MRSA, coagulase-negative staphylococci, streptococci and vancomycin-susceptible enterococci (VSE), but lacks efficacy against vancomycin-resistant enterococci (VRE) or staphylococci strains [14, 55]. Given the limited availability of direct test susceptibility to dalbavancin, in vitro susceptibility test to vancomycin is acceptable as a surrogate for susceptibility to dalbavancin [56]. Dalbavancin has a long plasma half-life of approximately 14 days mainly due to 93% protein binding, a predominantly non-renal clearance and a good tissue penetration in different sites of infection, with notable activity against bacterial biofilm [55, 57]. Importantly, no dosage adjustment is needed in patients with mild/moderate renal impairment or mild hepatic impairment [55].

Dalbavancin has currently received approval for the treatment of ABSSSI administered as a single intravenous dose 1500 mg or a 1000 mg dose followed by 500 mg 1 week later [55, 57]. In the DISCOVER 1 and 2 double-blind, multicenter, randomized trials (n = 1301 patients with ABSSSI, among which 13% had diabetes mellitus), once-weekly intravenous dalbavancin was non-inferior to twice-daily intravenous

vancomycin followed by oral linezolid [58]. Moreover, adverse events were less frequent in the dalbavancin group [58]. In another randomized, double-blind study, a single 1500 mg dose of dalbavancin was non-inferior to a two-dose regimen (1000 mg followed by 500 mg one week later) in patients with ABSSSI [59].

Given its unique pharmacokinetic and pharmacodynamic properties, there is interest in the use of dalbavancin beyond approved indications, including for outpatient parenteral antimicrobial therapy of infections caused by gram-positive bacteria, such as osteomyelitis, which is a frequent cause of "difficult-to-treat" diabetic foot infections. Indeed, in a randomized trial in 80 patients with osteomyelitis, treatment with dalbavancin (1500 mg administered on day 1 and 8) resulted in similar clinical cure rates compared with standard of care (97 and 88%, respectively), with no difference in tolerability between the two groups [60]. However, the duration of hospitalization was almost half in patients treated with dalbavancin (15.8 days vs. 33.3 days in the standard of care arm) [60]. Notably, 6% of patients in the dalbavancin group presented with diabetic foot infection [60]. Several observational studies also showed the efficacy and safety of dalbavancin in the treatment of bone and joint infections [57, 61–67]. In a recent retrospective study in 22 patients with diabetic foot infection who were treated with dalbavancin as a second choice therapy, the cure rate was 87% [68]. A case of successful treatment with dalbavancin of diabetic foot osteomyelitis caused by *Enterococcus faecium* was recently reported [70].

Oritavancin

Oritavancin is another novel synthetic lipoglycopeptide, similar in structure to vancomycin, and is approved for the management of ABSSSI. Oritavancin exhibits bactericidal activity against gram-positive pathogens, including MRSA, and is also active in vitro against VRE and vancomycin-resistant *S. aureus*, unlike dalbavancin [69]. Similar to dalbavancin, oritavancin has a long plasma half-life of 8–10 days, a high protein binding of 90% and slow kidney clearance, allowing for single-dose treatment [69]. No adjustment is needed in patients with mild or moderate renal insufficiency. However, oritavancin exerts weak inhibitory activity on the cytochrome P450, which can potentially lead to drug–drug interactions, especially with warfarin, and may artificially prolong activated partial thromboplastin time for up to 5 days [14, 69].

Two large, randomized, controlled trials (RCTs), SOLO-1 and -2, demonstrated that a single 1200 mg dose of oritavancin was non-inferior to twice-daily vancomycin for 7–-10 days for the treatment of ABSSSI caused by gram-positive pathogens [71, 72]. No significant differences in safety were noted [67, 68]. The most frequently reported adverse effects in the oritavancin group were nausea, headache, vomiting and diarrhea [71, 72]. In addition, transient transaminase elevations were noted in 2% of the patients but without signs of drug-induced liver injury [71, 72]. Of note, in the SOLO-2 study, five cases of osteomyelitis were reported as adverse events in the oritavancin group; therefore, osteomyelitis is listed as a warning for oritavancin, even though these events occurred within the first 9 days after drug initiation, suggesting that it may have been already present [69, 72]. However, retrospective data, case series and real-world data suggested that oritabancin is both safe and effective in the management of osteomyelitis [73–77]. Therefore, the role of this agent in the management of diabetic foot infection is currently unclear.

OXAZOLIDINONES

Tedizolid

Tedizolid is a second-generation oxazolidinone and is active against gram-positive microorganisms, including linezolid-resistant MRSA and VRE, as well as *Nocardia spp., Mycobacterium tuberculosis* and non-tuberculous mycobacteria [78]. Tedizolid has oral bioavailability > 90% and can be administered either intravenously or per os at a dose of 200 mg once daily because of a half-life of 12 h, which is longer than linezolid

[78]. It does not require dose modification in patients with renal or hepatic impairment [78].

Tedizolid is approved for the treatment of ABSSSI, based on evidence from two RCTs, ESTABLISH 1 and 2 [78]. In these studies, tedizolid 200 mg once daily for 6 days was non-inferior to linezolid 600 mg twice daily for 10 days for the treatment of ABSSSI, suspected or documented to be due to a gram-positive pathogen [79, 80]. The 6-day tedizolid course was well tolerated with less frequent gastrointestinal adverse events (nausea, diarrhea, vomiting) than linezolid as well as thrombocytopenia [79, 80]. Retrospective studies suggest that long-term tedizolid treatment is also well tolerated and is less frequently associated with hematological toxicity than linezolid [81, 82]. In a meta-analysis of 15 studies, tedizolid had superior clinical efficacy than vancomycin in ABSSSI caused by MRSA [83].

Since patients with diabetic foot infection were excluded from these two large trials, use of tedizolid in serious diabetic foot infections remains off-label but promising. According to a recent study that compared tedizolid pharmacokinetics and tissue penetration between diabetic patients with wound infections and healthy volunteers, the penetration into and exposure to tissue were similar in both groups, supporting the need for further evaluation of tedizolid use in diabetic foot infection [84]. Tedizolid appears promising in the treatment of more severe gram-positive infections, such as osteomyelitis, with some clinical trials underway, whereas data from smaller retrospective studies suggest good outcomes in osteoarticular and diabetic foot infections, with a cure rate of 83%, comparable to that of linezolid, and with a better safety profile [82, 85, 86].

CONCLUSION

Several antibiotics have been developed in the last decade, and some of them appear to hold promise as therapeutic options in patients with diabetic foot infection (Table 1). However, there

Table 1 Common pathogens in diabetic foot infection, antibiotics they are resistant to and novel antibiotics that might be useful in their management

Pathogen	Current treatment options with rising rates of resistance	Novel antibiotics that could be used for treatment
Staphylococcus aureus	Methicillin	Ceftaroline
	Vancomycin	Dalbavancin
	Daptomycin	Oritavancin
		Tedizolid
Pseudomonas aeruginosa	Piperacillin/tazobactam	Ceftazidime/avibactam
	Meropenem	Ceftolozane/tazobactam
		Cefiderocol
		Imipenem/cilastatin/relebactam
Enterobacteriaceae	Piperacillin/tazobactam	Ceftazidime/avibactam
	Meropenem	Ceftolozane/tazobactam
		Cefiderocol
		Meropenem/vaborbactam
		Imipenem/cilastatin/relebactam
		Plazomicin

are very limited data regarding the safety of these novel antibiotics in patients with diabetic foot infection, and randomized controlled studies in this field are lacking. Until more robust data are available, cefiderocol and dalbavancin, which have been studied more extensively in patients with bone infections, might be attractive options in carefully selected patients with severe diabetic foot infection. To avoid the emergence of resistance to these novel antibiotics, their use should be limited to patients with severe diabetic foot infection caused by bacteria susceptible only to these antibiotics and no other treatment options.

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