Diabetic foot infections: microbiological aspects, current and future antibiotic therapy focusing on methicillin-resistant *Staphylococcus aureus*

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ABSTRACT

Diabetic patients are at increased risk of complicated skin, skin structure and bone infections including infections of diabetic foot ulcerations (DFU). Analyses of epidemiology and microbial pathogenicity show that staphylococci seem to be predestined to induce such infections. In addition, multidrug resistance particularly due to an increasing prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) seems to be the challenge for effective antibiotic therapy. With regard to infections with MRSA, classical agents like vancomycin, linezolid, fosfomycin or trimethoprim–sulphametoxazol might be agents of choice in DFU. New-generation drugs including broad-spectrum tetracyclines like tigecycline, first and second generation of cyclic lipopeptides, anti-MRSA β-lactams including cefotibprrole and anti-MRSA antibodies are developed or in progress and the hope for the future.

Key words: Antibiotic therapy • Diabetic foot infection • MRSA

INTRODUCTION

It is estimated that approximately up to one quarter of all patients with type 2 diabetes mellitus will develop diabetic foot ulcerations (DFU) during their lifetime (1). Further studies have shown that the diabetic foot syndrome is not exclusively a classical late diabetic complication, but already often appears with newly diagnosed diabetic patients (2,3). Beside the emotional stress of a possible amputation attention should be paid to the increased mortality (4,5), where the mortality rate of people with diabetes and the diabetic foot syndrome are more than twice as high as that of the average population (6,7). The hospital mortality rate after a major amputation is 15–25% (4). A key factor is that 25% of the incurred diabetes costs to the community account for the diabetic foot syndrome, it is also responsible for almost...
half of the duration of the in-patient stay (8,9). Most DFU are colonised and infected with microorganisms, whereas approximately one quarter expands to deep soft tissue infections and bone infections. The cost for the treatment of foot ulcers depends on the disease severity like the presence or absence of peripheral arterial disease and infection. The Eurodiabe Study shows that the total treatment cost of patients with peripheral arterial disease and infection is around €16 835 in the 12 months after ulceration. That is almost four times as much as the cost for patients without peripheral arterial disease and infection (€4500) and is related to a higher rate of hospitalisation, higher costs of antibiotics, revascularisation and amputations (10). However, the optimum standard of care is always the complete pressure relief and wound debridement, wound dressings and measures to optimise glycaemic control such as switching to if necessary, improving peripheral circulation (angiography with percutaneous transluminal angioplasty or revascularisation), and appropriate antibiotic therapy (3,11–13).

The aim of this review is to present expert opinion and evidence from published literature on problems of anti-infective therapy of DFU. These problems are a result of immunological, microbiological aspects of DFU and an increased prevalence of multidrug resistance particularly due to methicillin-resistant Staphylococcus aureus (MRSA). Therefore, we performed a systematic research of MEDLINE using terms ‘diabetic foot’, ‘MRSA’, multidrug resistant organisms (‘MDRO’) and ‘antibiotic therapy’ alone and in combination for the main part of this review focusing on multidrug resistance and MRSA therapy.

IMMUNOLOGICAL AND MICROBIOLOGICAL ASPECTS COMPLICATING EFFECTIVE THERAPY

In addition to metabolic disorders, neuropathy and vasculopathy, immunological aspects also play a role in the pathogenesis of the DFU complicating its therapy. Generally, patients with diabetes show an increased risk of severe infections (14,15). Changes in the immunological function of polymorphonuclear granulocytes may play a role in the causation of DFU. These dysfunctions include changes in migration, phagocytosis, intracellular killing and chemotaxis (16). Other studies have shown that the specific cellular immune response is altered in diabetes, which can cause disturbances in granuloma formation, a delay and prolonged abscess formation and a disorder in the healing of the wound (17–20). Some of these immune deficiencies are directly related to metabolic disorders caused by poor glycaemic control.

In addition to the altered immune competence of the diabetic patient, pathogen-specific predictors play an important role in the infection of the diabetic foot. In newly formed ulcers, monoinfections due to staphylococci and β-haemolytic streptococci are observed most commonly, whereas in older ulcers with necrosis and previous antibiotic exposure, a polymicrobial flora with fecal characteristics predominates.

A differentiated view on pathogenicity and virulence factors shows that staphylococci, particularly S. aureus, seem to be predestined for soft tissue and bone infections. This becomes particularly apparent when analysing the infection process. The initial event at the beginning of an infection is the adhesion, which first reversibly comes about through ionic interaction and hydrophobicity between bacteria and tissue surface (21). The tissue surface includes protein structures, however, for which the microorganism has specific adhesins. The majority of S. aureus strains have adhesins for type I and II collagen, fibrinogen, laminin, fibronec tin, thrombospondin, bone sialoprotein (BSP) and heparan sulfate (22,23).

Furthermore, the synthesis and secretion of polysaccharides (glycocalyx) can play a role in the case of S. aureus and is also documented for strains obtained from DFU (24). The polysaccharide production begins immediately after the adhesion, wraps up the bacteria and is an essential component for the development of a ‘biofilm’. Behind this terminology, a structured conglomeration of bacteria, bacterial exoproducts and host proteins is hidden. The polysaccharide film is an essential component for pathogenicity and non healing, because it protects the pathogen against the effect of antibiotic therapy and the access of specific and non specific immunity (25–28). In the mouse model, biofilms seem to inhibit T and B-cell blastogenesis and chemotaxis, whereby the virulence of the pathogen is increased. Beyond that, immunogenic superficial bacterial
elements such as lipoteichoic acid or teichoic acid can be camouflaged by bacterial glyco-
calyx and thus counteract an opsonisation of pathogens. Studies of growth kinetics and mor-
phologies of bacteria have pointed out that the phenotype of the bacteria changes within a
biofilm (29–33). This shows that the bacte-
ria form at first microcolonies (‘small colony variants’) in which the bacterial metabolism is
reduced. The cells grow and the cellular wall
thickness increases. These changes can protect
against an antibiotic effect, as far as the bacteri-
cidal effect primarily occurs during the phases
of division and growth (e.g. β-lactam antibi-
otics). However, the antimicrobial resistance
of biofilm-forming agents is elucidated only
insufficiently. Perhaps it is based on chemi-
cal environment changes within the biofilm
(e.g. pH changes) in which antibiotics become
ineffective.

In addition to specific adherence mecha-
nisms staphylococci have a number of other
more or less non specific virulence factors,
which can be advantageous in the infection
of soft tissues and bones: S. aureus secretes
haemolysins which can lead to tissue necroses.
Furthermore, different proteases, collagenases
and hyaluronidases are produced that increase
the invasiveness of the organism. Some staphy-
lococcal strains encode virulence genes includ-
ing enterotoxins, toxic-shock syndrome toxin,
Panton–Valentine leukocidin, which seem to
be associated with high-grade infected dia-
betic ulcers and worse outcome (34). Proin-
flammatory cytokines (TNF-α, interleukin-1)
additionally can be released which can lead to
an increased osteoclast activity and strength-
ened matrix metalloproteinase activity in the
area of the bone (35).

INCREASING PROBLEM OF
MULTIDRUG RESISTANCE IN DFU
As mentioned above, Gram-positive bacteria
are commonly isolated from infected DFU.
Among these S. aureus predominates, and the
frequency of MRSA in hospitalised patients
is increasing during recent years from 5% up
to nearly 24% depending on geographical
distribution, type and severity of infection
(36–39). Data of recent studies from Asia
also recognised further MDRO beside MRSA
encoding for extended spectum β-lactamas-
es (ESBL) or new metallo-β-lactamas-
es (40,41).

Also MRSA dominates among MDRO in
these studies, Gram-negative microorganisms
like Escherichia coli, Acinetobacter spp. and
Pseudomonas aeruginosa were more com-
mon than Gram-positive bacteria changing an
old paradigm for DFU. A new metallo-
β-lactamase gene, blaNDM-1, was described in a
Klebsiella pneumoniae isolated from a com-
plexed skin and skin structure infection (CSSTI)
in a Swedish patient returning from India (42).
The broad resistance carried on this plasmid,
which is therefore transferable to recipient
strains, is a further worrying development
for Europe (43). In patients with DFU, deep
and recurrent ulcer, previous hospitalisation,
HbA1c level, nephropathy and retinopathy
seemed to be associated with MDRO including
MRSA (44,45).

With regard to the impact of MRSA com-
pared to methicillin-sensitive S. aureus (MSSA)
in DFU, the association to increased fre-
quency of treatment failure, longer time of
ulcer healing and higher risk of lower limb
amputation was proved by different studies.
Recent data have suggested that MRSA
isolation was linked to treatment failure in
patients with infected DFU (46). However,
among MRSA positive ulcers, treatment fail-
ure did not differ between those who were
handled with linezolid/daptomycin compared
to other antimicrobials. With regard to ulcer
healing time, data from studies are contradic-
tory: in one smaller study time of ulcer healing
was longer in MRSA-infected DFU compared
to MSSA (45), whereas two other studies did
not observe differences of healing rates (47,48).
Diabetic patients with lower limb amputations
had more frequently peripheral artery dis-
ease (PAD), osteomyelitis or infections with
MRSA (49). This finding was underlined by
further studies, in which patients with MDRO
or MRSA had more frequent amputations or
were at risk for amputations compared to non
MDRO infections (39,50).

THERAPY OF MRSA: CURRENT
CONCEPTS AND FUTURE
PERSPECTIVES
Maximising positive outcomes for serious
MRSA infections in DFU requires an aggres-
sive treatment approach. Although specific
approaches will depend upon many factors,
the common strategy should recognise the

Key Points

- In patients with DFU, deep
  and recurrent ulcer, previous hospitalisation, HbA1c level, nephropathy and retinopathy
  seemed to be associated with MDRO including MRSA.
- With regard to the impact of MRSA compared to methicillin-sensitive S. aureus (MSSA)
  in DFU, the association to increased frequency of treatment failure, longer time of ulcer
  healing and higher risk of lower limb amputation was proved by different studies.
- Diabetic patients with lower limb amputations had more frequently peripheral artery disease (PAD), osteomyelitis or infections with MRSA.
positive contribution of minimising complications while also focusing on rapid resolution of infection (overview Table 1).

Vancomycin in general has been, and still is, the mainstay of therapy for MRSA infections. However, there is growing concern that vancomycin is losing activity for MRSA infection as a result of the so-called ‘vancomycin creep’ defined as a progressive increase in the minimal inhibitory concentration (MIC) for isolates (80,81). Although vancomycin has a long clinical track record for treating complicated soft tissue infections, there is only one specific randomised study investigating the treatment of diabetic foot infections (62). In this study, 1 g vancomycin was administered every 12 h intravenously (i.v.) over 60 min during a 7–14 day course leading to an overall clinical success rate of 69%. Although 37% of patients treated with vancomycin or linezolid or semi-synthetic penicillins showed adverse events, no patient demonstrated an elevation in creatinine or decrease in creatinine clearance in this study.

Linezolid, the first oxazolidinone, can be an alternative to vancomycin. This drug inhibits protein synthesis at the ribosome level and may have a bactericidal (82) or bacteriostatic effect (51). In general, linezolid is well tolerated given orally or intravenously, but myelotoxicity and neurotoxicity are the major adverse events. Lactic acidosis, peripheral neuropathy and optic neuropathy are very uncommon, but potentially irreversible adverse consequences. In-vitro activity of linezolid against Gram-positive isolates including MRSA from diabetic foot infections were excellent (73). In addition, Linezolid demonstrates good tissue penetration and sufficient bacteriostatic and bactericidal activity against MRSA in vivo in diabetic foot infections, even when blood flow is impaired (82). In two randomised clinical trials treating diabetic foot infections, linezolid was compared to aminopenicillins (83) and one of the comparators to daptomycin (62). The clinical efficacy for linezolid in MRSA-infected foot infections was 67% in the daptomycin study, and 81% overall compared to aminopenicillins.

Trimethoprim–sulphamethoxazole (cotrimoxazol), a folate antagonist, might be an agent of choice in the treatment of MRSA especially in outpatients, since this drug can be given orally. Sulfonamides are bacteriostatic against S. aureus by inhibiting dihydropteroate synthase and blocking folate biosynthesis. A second step in the inhibition of folate biosynthesis is carried out by trimethoprim, a tetrahydrofolate reductase inhibitor. Nearly 98% of MRSA isolates from skin and wound infections are susceptible to trimethoprim–sulfamethoxazole as recently reported in different settings (63). However, no study exists on the clinical efficacy of trimethoprim-sulphamethoxazole in diabetic foot infections. One small-sized prospective randomised trial (n = 34) with doxycycline as comparator for outpatient skin and soft tissue infections in an area with high MRSA prevalence was published (84). In this study, the overall clinical failure rate was 9%, with all failures occurring in the trimethoprim–sulphamethoxazole group. In summary, trimethoprim–sulphamethoxazole is a second-line agent for treatment of MRSA infections in patients unable to receive more active drugs. If this drug is selected, infections with a high bacterial burden (high degree of infected necrotic tissue or abscesses) should be avoided.

Fosfomycin is a phosphonic acid derivate and acts in the first stage of peptidoglycan synthesis of the bacterial wall. It has a rapid bactericidal effect and a wide spectrum of activity with a cumulative susceptibility rate of 87.9% for MRSA (66). Clinical information regarding the use of fosfomycin in MRSA is very limited and is inadequate in several ways: studies are retrospective, the number of reported cases is small or fosfomycin is frequently used in association with a second antibiotic agent such as aminoglycoside, penicillin or cephalosporin. However, pharmacokinetic–pharmacodynamic studies in patients with diabetic foot syndrome have shown a high fosfomycin concentration in bone (67) and good penetration into inflammatory lesions (61). Fosfomycin has a low rate of adverse events, which include mild gastrointestinal disturbances, phlebitis and pain at the injection site. The main drawback of fosfomycin is the rapid development of drug resistance.

Synercid is a streptogramin antimicrobial resulting from a combination of semisynthetic pristamycin derivates – quinopristin and dalfopristin – in a 3:7 ratio. It targets both early and late stages of protein synthesis resulting in an in-vitro activity of >90% against a high proportion of community and hospital-acquired MRSA strains (85,86). However, synercid has no regulatory approval by the Food and Drug
### Table 1 Overview on classic, alternative and future anti-methicillin-resistant Staphylococcus aureus (MRSA) agents for therapy of diabetic foot infections

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pharmacological class</th>
<th>Mode of administration</th>
<th>In-vitro efficacy on MRSA (%)</th>
<th>Clinical efficacy (%) in severe skin and skin structure infections (CSSTs)</th>
<th>Clinical efficacy (%) in diabetic foot infections</th>
<th>Side effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>Glycopeptide</td>
<td>i.v.</td>
<td>&gt;95</td>
<td>88–93</td>
<td>70</td>
<td>Nephrotoxicity, ototoxicity, thrombophlebitis, exanthema, neutropenia, thrombopenia</td>
<td>51–60</td>
</tr>
<tr>
<td>Fosfomycin</td>
<td>Phosphonic acid</td>
<td>i.v./i.m.</td>
<td>87.9</td>
<td>No data</td>
<td>No data</td>
<td>Gastrointestinal disturbances, phlebitis</td>
<td>61</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Oxazolidinone</td>
<td>i.v./oral</td>
<td>&gt;95</td>
<td>68–92.2</td>
<td>67–81</td>
<td>Bone marrow suppression, neurotoxicity, lactic acidosis</td>
<td>51,62,63</td>
</tr>
<tr>
<td>Synercid</td>
<td>Streptogramin</td>
<td>i.v.</td>
<td>&gt;90</td>
<td>68.2</td>
<td>No data</td>
<td>Arthralgia, myalgia</td>
<td>64,65</td>
</tr>
<tr>
<td>Trimethoprim–</td>
<td>Sulphamethoxazole</td>
<td>i.v./oral</td>
<td>&gt;95</td>
<td>79</td>
<td>No data</td>
<td>Gastrointestinal effects, glossitis, stomatitis, erythema, myelosuppression</td>
<td>66,67</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Cyclic lipopeptide</td>
<td>i.v.</td>
<td>&gt;95</td>
<td>77</td>
<td>66</td>
<td>Nausea, headache, skeletal muscle side effects, headache, nausea, dizziness, gastrointestinal effects, anaphylactoid reactions</td>
<td>51,68–70</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Tetracycline derivate</td>
<td>i.v.</td>
<td>&gt;95</td>
<td>78.1–81.4</td>
<td>No data</td>
<td>Nausea, headache, diaphoresis</td>
<td>59,72,77</td>
</tr>
<tr>
<td>Dalbavancin</td>
<td>Lipoglycopeptide</td>
<td>i.v.</td>
<td>&gt;95</td>
<td>88.9</td>
<td>No data</td>
<td>Nephrotoxicity, nausea, diaphoresis</td>
<td>73,74</td>
</tr>
<tr>
<td>Telavancin</td>
<td>Lipoglycopeptide</td>
<td>i.v.</td>
<td>&gt;95</td>
<td>80–96</td>
<td>No data</td>
<td>Nausea, headache, taste disturbances, insomnia</td>
<td>52,75</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>Lipoglycopeptide</td>
<td>i.v.</td>
<td>&gt;95</td>
<td>82</td>
<td>No data</td>
<td>Nephrotoxicity, diaphoresis, fever</td>
<td>53</td>
</tr>
<tr>
<td>Ceftobiprole</td>
<td>Pyrrolidinone</td>
<td>i.v.</td>
<td>&gt;95</td>
<td>93</td>
<td>86</td>
<td>Taste disturbances, headache</td>
<td>59,76,77</td>
</tr>
<tr>
<td>Cefaroline</td>
<td>N-phosphoamino</td>
<td>i.v.</td>
<td>&gt;95</td>
<td>85.9</td>
<td>No data</td>
<td>Nausea, headache, insomnia</td>
<td>60</td>
</tr>
<tr>
<td>Iclaprim</td>
<td>Diaminopyrimidine</td>
<td>i.v./oral</td>
<td>&gt;95</td>
<td>92.9</td>
<td>No data</td>
<td>Pruritus, erythema</td>
<td>78</td>
</tr>
<tr>
<td>Tefibazumab</td>
<td>Anti-clumping factor monoclonal antibody</td>
<td>i.v.</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Nausea, headache, neutropenia</td>
<td>79</td>
</tr>
</tbody>
</table>

i.v., intravenous; i.m., intramuscular.
Administration (FDA) for the treatment of MRSA, and no clinical study on the effect in diabetic foot has been conducted. In treatment studies of hospitalised patients with complicated Gram-positive skin and skin structure infections, the clinical success rate for synergy was 68.2% and therefore comparable to the comparator group (64).

Daptomycin is a cyclic lipopeptide in clinical use and approved for the treatment of CSSTI including the diabetic foot (62). Daptomycin causes a calcium-dependent rupture of the bacterial cell membrane resulting in a net efflux of potassium that inhibits DNA, RNA and protein synthesis (65). It is active against staphylococci including MRSA, and other Gram-positive bacteria (68,87). Resistance to daptomycin is uncommon, but can be induced by serial passage in increasing concentrations of the antimicrobial. Clinically, it has occurred in patients who have received prolonged treatment. Daptomycin is only available for intravenous administration and requires dose reduction in patients with renal failure. In a clinical study in diabetic patients with *S. aureus* bacteremia and/or endocarditis comparing daptomycin with an anti-staphyloccal penicillin or vancomycin plus gentamycin, renal dysfunction occurred more frequently in patients receiving vancomycin than in those receiving daptomycin (26% versus 11%) (69). In patients with infected diabetic ulcers, daptomycin had a clinical success rate of 66%, similar to the 70% of the comparator (62). However, in this study the prevalence of MRSA was too low to draw any conclusions about the relative efficacy of daptomycin against this pathogen. In a randomised trial in non diabetic patients, the clinical success rate in CSSTIs with MRSA was 77% (88).

Dalbavancin is a second generation lipoglycopeptide with unique pharmacokinetic properties that allow dosing once-weekly (70). The dosage of dalbavancin is 1000 mg intravenously initially, and 500 mg 7 days later. The in-vitro activity against aerobic and anaerobic isolates including MRSA from DFU is excellent (73), but clinical data from diabetic patients are missing. In a randomised, double-blind study of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of CSSTIs, dalbavancin was as well tolerated and effective as linezolid given for 14 days (74).

Telavancin and oritavancin are second generation glycopeptides with multifunctional mechanisms of action and a good in-vitro activity against MRSA, VanA-type enterococci (telavancin) or MRSA and VanA-, B- and C-type enterococci (oritavancin). However, both antimicrobials are studied in CSSTIs in phase II/III studies with vancomycin as comparator (52,53,75). Among patients with MRSA, clinical cure rate was 96% for telavancin compared to 90% for vancomycin, but no inferiority for oritavancin. No data are available for diabetic patients yet.

Tigecycline is a new broad-spectrum tetracycline derivative (glycocycline) being developed to overcome bacterial mechanisms of tetracycline resistance such as ribosomal protection and efflux pump. Tigecycline has potent in-vitro activity against a broad range of Gram-positive and Gram-negative bacteria including MRSA (71,89). Tigecycline can be administered only via the parenteral route, initially in a single dose of 100 mg, and then in doses of 50 mg every 12 h. There are two animal studies on the effect of tigecycline on MRSA osteomyelitis, one with teicoplanin as a comparator and the second with vancomycin (with or without rifampicin) (72,90). In both studies, tigecycline showed a high infection cure rate, but no inferiority to the comparators. In a susceptibility testing study on bacterial strains isolated from diabetic foot infections, tigecycline was active against 97.3% of Gram-positive cocci in particular MRSA (96%) (54). Although studies on the clinical efficacy of tigecycline in diabetic foot infections are ongoing, tigecycline is FDA-approved for the treatment of CSSTI (55-58). Tigecycline was compared with vancomycin–aztreonam combination in adults with CSSTIs (defined by polymicrobial aetiology, need for surgical intervention, suspected or confirmed deep soft tissue involvement and/or comorbidities such as diabetes mellitus, peripheral vascular disease or peripheral neuropathy). The primary end-point was clinical response at the test-of-cure (TOC) visit (12–92 days after end of treatment). Clinical cure rates were equivalent between the two treatment groups. In this study, the overall eradication rates for MRSA strains were reported as 78.1% and 75.8% of tigecycline and vancomycin–aztreonam treated patients, respectively. Based on these results, tigecycline was non inferior to vancomycin–aztreonam combination in the treatment of CSSTI.
The classic concept that an MRSA isolate is an isolate with cross-resistance to all β-lactam drugs is no longer true. Several β-lactam agents are undergoing clinical trials, and will soon be added to the therapeutic armamentarium for MRSA infections in the diabetic foot. Ceftobiprole is a new cephalosporin administered intravenously with a good activity against Gram-negative bacteria (including a high proportion of Pseudomonas aeruginosa strains) (71,76) and against Gram-positive bacteria including nosocomial and community acquired MRSA (59). In a multicenter, multinational, double-blind, randomised trial concerning treatment of CSSTIs caused by Gram-positive bacteria, ceftobiprole was compared to vancomycin (77). Overall, 93% of those treated with ceftobiprole or vancomycin, respectively, were cured. The cure rates for patients with MRSA infections were 91.8% with ceftobiprole and 90.0% with vancomycin. In patients with diabetic foot infections sub-analysed from a second trial on the effect of ceftobiprole in CSSTIs, the clinical cure rate with ceftobiprole monotherapy was 86%, as effective as vancomycin plus ceftazidime (60).

Ceftaroline is also a novel cephalosporine with broad-spectrum activity including MRSA. Two randomised, observer-blinded studies to evaluate the safety and efficacy of ceftaroline versus standard therapy with vancomycin plus aztreonam in adults with CSSTIs showed comparable cure rates of 85-9% for ceftaroline or standard therapy as well as in patients with MRSA (91). The rates of adverse events were similar between the treatment groups with a safety profile of ceftaroline consistent with that of the cephalosporin class.

Iclaprim, a novel diaminopyrimidine, specifically and selectively inhibits bacterial dihydrofolate reductase, a key enzyme in the bacterial folate pathway (92). Iclaprim has, therefore, an extended spectrum of activity against important causative multiresistant pathogens such as MRSA, vancomycin-resistant S. aureus (VRSA), quinolone-resistant and trimethoprim-resistant Gram-negative strains (78). Iclaprim is available for intravenous and oral use, with very good oral bioavailability. A Phase II clinical trial has shown promise for use in CSSTIs that are caused by MRSA (93).

Tefibazumab is a monoclonal antibody that recognises clumping factor A on the surface of S. aureus (94). It is under development as adjunctive therapy for serious S. aureus infections, but additional trials are warranted to address the dosing range and efficacy of tefibazumab (79).

CONCLUSION
In recent years, a marked increase in the incidence of diabetic foot infections caused by MRSA has occurred. However, beside the microbial and clinical characteristics of DFU, problems of the effectiveness and limitations of drugs classically used for the treatment of MRSA were obvious. Newer anti-MRSA antimicrobials, for example, second generation glycolipopeptides, tigecycline and β-lactams have occurred in the clinical setting of CSSTIs. These agents are all clinically effective with promising pharmacodynamic properties, and studies in diabetic patients should be on demand now addressing effectiveness and limitations.

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Key Points
- In recent years, a marked increase in the incidence of diabetic foot infections caused by MRSA has occurred
- however, beside the microbial and clinical characteristics of DFU, problems of the effectiveness and limitations of drugs classically used for the treatment
- newer anti-MRSA antimicrobials, for example, second generation glycolipopeptides, tigecycline and β-lactams have occurred in the clinical setting of CSSTIs
- these agents are all clinically effective with promising pharmacodynamic properties, and studies in diabetic patients should be on demand now addressing effectiveness and limitations of MRSA were obvious


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Current and future antibiotic therapy of MRSA in diabetic foot


