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What's new on the antimicrobial horizon?

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ABSTRACT

The antimicrobial era is threatened by high levels of antibiotic resistance, the limited number and disparate availability of effective antibiotics against diverse bacterial species, and reduced involvement by the pharmaceutical industry in the development of new anti-infectives. For the treatment of resistant Gram-positive coccal infections, particularly methicillin-resistant staphylococcal infections, vancomycin has long been the mainstay antimicrobial agent due to its safety, durability against resistance, and lack of other approved alternatives. However, the efficacy and safety of vancomycin for the treatment of many serious infections has been called into question. Promising results from clinical trials suggest that five new antimicrobials could offer safe and effective alternatives to vancomycin. With regard to resistant Gram-negative infections, new carbapenems and some other options will be available. This paper reviews the safety and efficacy of these new antimicrobial agents against resistant bacterial pathogens.

1. Introduction

Methicillin, a β-lactam analogue, was developed in 1960 and demonstrated bactericidal activity against penicillin-resistant bacterial infections. Subsequently, methicillin-resistant staphylococci were detected in Europe in the late 1970s and in the USA by the late 1980s. The antibiotic era is threatened by a convergence of three adverse developments. The first is growing evidence of high levels of antibiotic resistance among important pathogens, including vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-intermediate/resistant *S. aureus* (VISA/VRSA), and multidrug-resistant (MDR) *Pseudomonas aeruginosa*, which have emerged in the past 20 years. The second is the limited number and disparate availability of classes of effective antibiotics against diverse bacterial species. The final concern is a reduction in the number of pharmaceutical companies pursuing research and development of new anti-infectives since 1985. [1]

In community settings in the USA, high or intermediate levels of penicillin resistance are estimated at a rate of 50% among strains of pneumococci. Similarly, 50% of *S. aureus* isolates are methicillin-resistant and 30% of enterococci are vancomycin-resistant in hospitals. [1] There are no effective antimicrobial agents for the treatment of the increasingly prevalent multi-resistant *Acinetobacter baumannii* strains. In addition, more than 25% of enterococcal strains associated with infections in patients in hospital intensive-care units are resistant to vancomycin and other antibiotics. [2] Among different strains of *P. aeruginosa*, 20% are resistant to quinolone agents and 15% are resistant to imipenem. [1] There is also a growing incidence of bacterial strains, such as *S. aureus*, with intermediate resistance to vancomycin (VISA) and complete resistance to vancomycin (VRSA). [1,2]

In addition to the evidence for increasing levels of antibiotic resistance among diverse pathogens, few new antimicrobial agents are in development, probably due to relatively unfavourable returns on investment. Four new classes of antibiotics were introduced in the 1930s and 1940s, including sulphonamides, β-lactams, aminoglycosides, and chloramphenicol. A further six classes were developed and approved in the 1950s and 1960s, including tetracycline, macrolides, glycopeptides, rifamycins, quinolones, and trimethoprim. However, from 1970 to the late 1990s, no new antimicrobial classes were approved and only a few new classes have been approved since 2000 for the treatment of Gram-positive infections; these are the oxazolidinones (linezolid), cyclic lipopeptides (daptomycin), and glycylcyclines (tigecycline). Pharmaceutical companies are discouraged from research and development of new antimicrobials due to high direct costs, risk, and the time associated with animal and in vitro studies. [1]

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Increasing levels of antibiotic resistance, the waning drug development pipeline, and declining numbers of pharmaceutical companies involved with the development of anti-infective agents create a significant public health threat to the effective management of bacterial infections. [1] Additional factors [2] that establish the imperative for the development of new antibiotics include:

(1) Emergence of bacterial species resistant to new antibiotics; species such as *P. aeruginosa* were initially considered to be effectively treated with β-lactam antibiotics but have since been shown to be less susceptible due to their ability to develop efflux pumps that can expel β-lactams from the cytoplasmic space.
(2) Intolerance to, or safety concerns about, treatment with currently available antibiotics, such as an increased risk of bleeding associated with linezolid.
(3) Current dosing regimens for most available antimicrobials that are incompatible with outpatient administration, resulting in prolonged hospital stay, increased cost, and increased exposure to nosocomial infections.

There is a need for new antimicrobial agents for the treatment of human pathogens that are not susceptible to currently available antibiotics. [1,2] These development efforts must be coordinated with aggressive infection control efforts and rational use of currently available and emerging antimicrobial agents. [2]

2. Limitations of vancomycin

Vancomycin was developed more than 50 years ago and has been the mainstay of treatment for a variety of infections, including endocarditis, pneumonia, and wound infections, with cure rates estimated at 63%, 75%, and 90% of patients, respectively. [3] However, there is growing evidence of clinical failure of vancomycin in the treatment of a variety of infections. In one study, analysis of outcomes among patients with infective endocarditis revealed a 42% failure rate in patients with methicillin-susceptible *S. aureus* (MSSA), resulting in a recommendation that vancomycin be used in combination with other antimicrobial agents to yield the best clinical results. [4]

In a retrospective study by Small and Chambers, [5] 5 of 13 intravenous drug users with *S. aureus* endocarditis who received vancomycin as their primary therapy had either a relapse or a complicated clinical course. Time-kill studies comparing vancomycin with nafcillin for 10 isolates of MSSA endocarditis have shown that vancomycin is less effective than nafcillin, with a failure rate of 38% compared with 1.4%. [5]

Nafcillin has also demonstrated superiority to vancomycin for the treatment of MSSA bacteraemia. One study enrolled 505 patients with *S. aureus* bacteraemia treated with either vancomycin or nafcillin and followed the patients for 3 years to determine infection recurrence rates. Analysis of recurrence rates revealed that 9.4% of all patients experienced a recurrence of infection, but that recurrence was significantly less frequent for patients treated with nafcillin (0%) than for patients receiving vancomycin (19%) ($P = 0.058$). [6]

In a retrospective analysis of two randomized, double-blind studies that enrolled 544 patients with suspected Gram-positive ventilator-associated pneumonia (VAP), the effect of linezolid (600 mg) vs. vancomycin (1 g q12h for 7–21 d) plus aztreonam was evaluated. Clinical cure rates for patients with MRSA VAP ($N = 70$) were 62.2% for the linezolid group, compared with 21.2% for patients treated with vancomycin ($P = 0.001$) and cure rates for all cases of VAP, confirmed Gram-positive VAP, and *S. aureus* VAP also favoured linezolid (45.4% vs. 36.7%, $P = 0.07$; 53.7% vs. 37.7%, $P = 0.02$; 48.9% vs. 35.2%, $P = 0.06$, respectively). [8]

Table 1. The FDA's updated vancomycin breakpoints for *Staphylococcus aureus* [7]

	Minimum inhibitory concentration (MIC) μg/mL		
	Susceptible (S)	Intermediate (I)	Resistant (R)
Updated	≤2	4–8	≥16
Previous	≤4	8–16	≥32

Factors contributing to the clinical failure of vancomycin include evidence of slower bacterial clearance in response to treatment with vancomycin, poor pharmacokinetic properties, and fluctuating minimum inhibitory concentrations (MICs). Poor pharmacokinetic properties undermining the efficacy of vancomycin include variable tissue penetration and high inoculum sizes. [9,10] Several studies have reported that the penetration of vancomycin into lung tissue is especially poor. [11–13] Vancomycin was shown to achieve bactericidal activity within 32 h of administration for low inoculum sizes but failed to demonstrate bacterial killing at 72 h following administration in high-inoculum MRSA. [14] Furthermore, the minimum bactericidal concentration (MBC) of vancomycin has steadily increased for the past several decades. In response to this, the United States Food and Drug Administration (FDA) has lowered the susceptibility breakpoints for staphylococcal infections (Table 1). [7] The MBC:MIC ratio determines the bactericidal effects of antimicrobials, with a ratio of 4:8 considered to be bacteriostatic. [9] Statistically significant associations have been confirmed between treatment failure and higher vancomycin MIC levels ($P = 0.02$) as well as reductions in bacterial kill rates in vitro over 72 h of incubation ($P = 0.03$), with the highest bactericidal levels reported for bacterial killing within 72 h. [15]

Vancomycin is also associated with several other limitations, including the development of resistance and associated therapeutic failure, and the potential for serious toxicity. There is growing evidence of vancomycin resistance, including vancomycin-intermediate *S. aureus* (VISA) and heterogeneous VISA, in patients with serious infections. Heterogeneous VISA infections are associated with high treatment failure rates, prolonged bacteraemia, high bacterial loads, and lower vancomycin trough levels. [9,10]

An additional concern about vancomycin includes adverse reactions, especially nephrotoxicity, when combined with aminoglycoside agents. Such reactions are provoked by vancomycin, especially among patients with high vancomycin trough concentrations compared to those with low trough concentrations (12% vs. 0%; $P = 0.01$) and patients with co-morbid renal disease. [16,17] Vancomycin has also been shown to provoke hypersensitivity reactions, including anaphylaxis and 'red man syndrome' (an infusion-related reaction involving pruritus and an erythematous rash). [10] The incidence of red man syndrome is estimated to be between 3.7% and 47%, with higher rates evident in patients younger than 40 years.

Although vancomycin has been considered to be the reference standard for the treatment of invasive MRSA infections for several decades, recent data on the efficacy and safety limitations of vancomycin, combined with the advent

and testing of new compounds with anti-MRSA activity, call into question the efficacy of vancomycin for the treatment of many serious infections. [18]

3. New antibiotics with efficacy against MRSA

Table 2 lists five classes of new antimicrobials with efficacy against MRSA that are in development. [18] Additional details about these agents are provided in the following subsections.

Table 2. New antibiotics for the treatment of methicillin-resistant *Staphylococcus aureus* [18]

Class	Antibiotics	Remarks
Glycopeptides	Dalbavancin	Once-weekly dosing
	Telavancin	Once-daily dosing
	Oritavancin	Once-daily or every other day dosing
Lipopeptide	Daptomycin	cSSTI, endocarditis (not for pneumonia)
Cephalosporin	Ceftobiprole	Broad spectrum
	Ceftaroline	Broad spectrum
Diaminopyrimidine	Iclaprim	
Glycylcycline	Tigecycline	Broad spectrum

cSSTI: complicated skin and soft tissue infection.

3.1. Glycopeptides

New glycopeptide agents include dalbavancin and telavancin, which are suitable for the treatment of MRSA and VISA strains and exhibit activity against a variety of other organisms (Table 3). [19,20] Dalbavancin is a semi-synthetic lipoglycopeptide derived from a teicoplanin-like glycopeptide agent (A40926). [19] It inhibits cell wall synthesis and has in vitro activity against MRSA with a long half-life of 6–10 d that allows once-weekly dosing. [18]

A phase 3 non-inferiority trial of 854 patients with complicated skin and skin structure infections, including those suspected of involving MRSA, was conducted to compare the efficacy of intravenous (i.v.) dalbavancin 1,000 mg on day 1 and 500 mg on day 8 with linezolid 600 mg i.v. infusion q12h for 14 d. Dalbavancin demonstrated similar cure rates when compared with linezolid. The clinical success rate for dalbavancin was 88.9% compared with 91.2% for linezolid, which confirmed the non-inferiority of dalbavancin. Relapse rates were less than 1% for both treatment arms. Both treatment regimens were well tolerated, and the most frequent adverse events (AEs) reported were gastrointestinal side-effects for both agents. The overall rate of AEs was higher for patients treated with linezolid (32.2%) than for patients given dalbavancin (25.4%). [20]

Table 3. New glycopeptides with in vitro activity against a variety of Gram-positive organisms [19,20]

Organism	MIC_{90} (mg/L)	
	Dalbavancin	Telavancin
Staphylococcus aureus		
MSSA	0.06–0.5 (N = 4,838)	0.5–1.0 (N = 77)
MRSA	0.06–1.0 (N = 2,726)	0.5–2.0 (N = 158)
GISA	1.0–2.0 (N = 29)	4 (N = 37)
Enterococcus faecalis		
Vancomycin-susceptible	0.06 (N = 586)	1.0–2.0 (N = 458)
Vancomycin-resistant	32.0 (N = 34)	4.0–16.0 (N = 50)
Enterococcus faecium		
Vancomycin-susceptible	0.12 (N = 77)	0.25–0.5 (N = 120)
Vancomycin-resistant	32.0 (N = 92)	4.0–8.0 (N = 267)
Streptococcus pneumoniae	⩽0.03–<0.06 (N = 1,422)	0.015–0.03 (N = 412)

MSSA: methicillin-sensitive *S. aureus*; MRSA: methicillin-resistant *S. aureus*; GISA: glycopeptide-intermediate *S. aureus*; MIC: minimum inhibitory concentration.

Dalbavancin provides an alternative for the treatment of resistant Gram-positive infections, including MRSA. Results from studies that enrolled more than 1,000 patients in phase 2 and 3 trials confirm the safety of dalbavancin, with the most commonly reported adverse events including nausea, diarrhoea, and constipation with some evidence suggesting an increased risk of hypotension, hypokalemia, and increased levels of alanine aminotransferase and aspartate aminotransferase. [18,19] The once-weekly treatment regimen offers patients greater convenience and is possibly more cost-effective. [19]

Telavancin is an investigational lipoglycopeptide antimicrobial agent with a dual mechanism of action that inhibits cell wall synthesis and disrupts membrane barrier function. Its half-life ranges from 7 to 9 h, which permits once-daily dosing at 7.5–10 mg/kg/day. Disruption of the membrane barrier function permits rapid bactericidal activity for a variety of pathogens including MRSA and other drug-resistant strains of streptococci, enterococci, and staphylococci. Telavancin is also active against Gram-positive aerobic and anaerobic organisms. In vivo studies have demonstrated that telavancin may be effective for the treatment of Gram-positive soft-tissue infections, bacteraemia, endocarditis, meningitis, and pneumonia. Furthermore, the MIC of telavancin is generally 2–8 times less than that of vancomycin for many Gram-positive bacteria, including MRSA. [21]

A randomized, double-blind, controlled, phase 2 trial enrolled 167 patients with complicated skin and soft-tissue infections and randomized patients to either telavancin i.v. once daily, or an anti-staphylococcal penicillin four times daily, or vancomycin twice daily. Telavancin resulted in cure rates at test-of-cure of 80% for patients with *S. aureus*, compared with 77% for those treated with standard antimicrobial regimens. Cure rates at test-of-cure in response to telavancin were 84% compared with 74% for patients with MRSA infections, although this difference was not statistically significant. [22]

Telavancin also appears to be more effective for the treatment of MRSA infections than vancomycin. A second phase 2, randomized, double-blind, active-controlled trial enrolled 195 adults with skin and skin structure infections at 11 centres in the USA and seven facilities in South Africa. Patients were randomized in a 1:1 ratio to treatment with either telavancin 10 mg/kg q24h or standard intravenous therapy (either vancomycin 1 g q12h, nafcillin 2 g q6h, or cloxacillin 0.5–1 g q6h). Comparable cure rates of 96% and 94% were reported for telavancin and standard therapy, respectively. However, cure rates at test-of-cure were significantly higher for the telavancin arm (94%) compared with standard antimicrobial treatments (83%; P = 0.06). Eradication at test-of-cure was significantly higher for the telavancin group (92%) vs. those treated with standard agents (78%; P = 0.07), and patients with MRSA had eradication rates of 92% in response to telavancin compared with 68% for those administered the three standard regimens (P = 0.04). A summary of the microbiological response rates for all patients

Table 4. Results from a phase 2 randomized, double-blind, active-controlled trial – FAST 2. [23]

	Response rate (%)		*P*-value
	Telavancin[a]	Standard therapy[b]	
Clinical response	96.0	94.0	0.53
Microbiological response			
Overall	89.0	77.0	0.09
Staphylococcus aureus	92.0	78.0	0.07
MRSA cases	92.0	68.0	0.04

MRSA: methicillin-resistant *Staphylococcus aureus*.

[a] Telavancin 10 mg/kg q24h.

[b] Either intravenous vancomycin 1 g q12h, nafcillin or oxacillin 2 g q6h, or cloxacillin 0.5–1.0 g q6h.

and those with either *S. aureus* or MRSA is presented in Table 4, demonstrating that telavancin achieved higher cure rates overall and for *S. aureus* and MRSA. [23]

3.2. Lipopeptides

Daptomycin is a cyclic lipopeptide that depolarizes the bacterial cell membrane. It is a fermentation product of *Streptomyces roseosporus* consisting of a 13-member amino acid cyclic lipopeptide with a decanoyl side chain. [18,24] The recommended dose is 4 mg/kg once daily for patients with skin and skin structure infections and 6 mg/kg once daily for bloodstream infections, including right-sided endocarditis. [18] Daptomycin has established efficacy for the treatment of a broad range of Gram-positive aerobic and anaerobic bacteria, although it is not an effective antimicrobial for the treatment of Gram-negative bacteria. [24]

Two phase 3, multicenter, randomized, controlled, blinded trials enrolling 1,092 patients from 65 clinical centres in the USA, 25 in South Africa, 42 European sites, five sites in Australia, and three sites in Israel provide a comparison of the efficacy and safety of daptomycin with conventional antimicrobials, including penicillinase-resistant penicillins and vancomycin, for the treatment of hospitalized patients with complicated skin and skin structure infections. For the intent-to-treat population, clinical success rates were comparable between daptomycin and standard treatment groups (71.5% vs. 71.1%, respectively). Among the 902 clinically evaluable patients, success rates were also similar at 83.4% in the daptomycin arm and 84.2% in the comparator arm ($P > 0.5$). Similarly, clinical response rates for the daptomycin and conventional antimicrobial treatment regimens were comparable for evaluable patients with Gram-positive infections. For example, 76% of patients treated with daptomycin who had both *S. aureus* and β-haemolytic streptococcal infection had clinical success compared with 70% of those treated with comparator antibiotics. Relapse rates were not significantly different between patients considered to have had a clinically successful response at the test-of-cure visits, with 4.2% of those treated with daptomycin experiencing a relapse or recurrence compared with 5.5% of those administered a comparator antibiotic. [25]

The duration of treatment was significantly shorter for patients who achieved clinical success, with 67% of the patients in the daptomycin group requiring only 4–7 days of treatment vs. 33% of those in the comparator groups ($P < 0.0001$). The safety and tolerability of daptomycin were comparable with the other treatment arms, with 18% of daptomycin-treated patients experiencing one or more adverse events related to the study treatment compared with 21% of patients in the other treatment groups. Treatment discontinuation rates were comparable between all study groups and were less than 3%. [25]

In an open-label, randomized trial of 124 patients with *S. aureus* bacteraemia, with or without endocarditis, randomly assigned to treatment with daptomycin 6 mg/kg by intravenous infusion or low-dose gentamicin plus either anti-staphylococcal penicillin or vancomycin, success rates were 44.2% for the daptomycin arm vs. 41.7% for the alternative treatment groups, demonstrating the non-inferiority of daptomycin. There were no statistically significant differences in treatment success rates between patients with complicated bacteraemia, right-sided endocarditis, and MRSA between the different treatment arms. [26] These results supported the FDA approval of daptomycin in 2003 for skin and skin structure infections and for the treatment of bacteraemia and right-sided endocarditis in 2006, although daptomycin is not indicated for the treatment of pneumonia. Phase 3 clinical trials of hospitalized patients with community-acquired pneumonia failed to demonstrate efficacy for daptomycin compared with ceftriaxone 2 g q24h, with clinical efficacy rates of 79% for daptomycin and 87% for ceftriaxone. The lower efficacy of daptomycin was attributed to interactions between daptomycin and pulmonary surfactant, which inhibits its antibacterial effects. [27]

3.3. Ceftobiprole

Ceftobiprole is an extended-spectrum cephalosporin that has demonstrated significant activity against Gram-negative and Gram-positive pathogens. [18,28] It is especially effective for the treatment of β-lactam-resistant Gram-positive infections including MRSA, penicillin-resistant *Streptococcus pneumoniae*, and ceftriaxone-resistant *S. pneumoniae*. This agent binds to penicillin-binding proteins (PBPs), an important factor that enhances its bactericidal ability. Ceftobiprole binds tightly to the active site of PBP2′ and rapidly forms a stable acyl-enzyme complex. This interaction results in very slow hydrolysis of the molecule that, in turn, results in the stable inhibition of this enzyme. [28] The agent is administered intravenously and has been granted fast-track approval status by the FDA. [18] Ceftobiprole also appears to have a favourable safety profile with no clinically relevant safety events reported in trials that have enrolled almost 500 patients. [28]

The MIC of ceftobiprole compared with those for linezolid, quinupristin–dalfopristin, vancomycin, and daptomycin was evaluated for several different organisms including methicillin-sensitive *S. aureus* (MSSA), MRSA, methicillin-sensitive coagulase-negative staphylococci (MS-CNS), and methicillin-resistant coagulase-negative staphylococci (MR-CNS). Among 152 *S. aureus* (including five VISA and two VRSA) strains, MIC_{50} and MIC_{90} values for ceftobiprole were each 0.5 μg/mL against MSSA and 2 μg/mL against MRSA. Among 151 coagulase-negative staphylococci (including four vancomycin-intermediate strains), MIC_{50} and MIC_{90} values for ceftobiprole were 0.125 μg/mL and 1 μg/mL, respectively, against MS-CNS strains and 1 μg/mL and 2 μg/mL, respectively, against MR-CNS strains. [29] Ceftobiprole has also demonstrated strong in vitro activity against Gram-negative bacteria, including *Escherichia coli*, *Klebsiella*

Table 5. Ceftobiprole in vitro activity against staphylococci [29]

Organism	MIC_{90} (μg/mL)				
	Ceftobiprole	Linezolid	Quin/dalfo	Vancomycin	Daptomycin
Methicillin-sensitive *Staphylococcus aureus*	0.5	2.0	0.5	1.0	0.5
Methicillin-resistant *S. aureus*	2.0	2.0	0.5	1.0	0.5
Methicillin-sensitive coagulase-negative staphylococcus	1.0	2.0	0.25	2.0	0.5
Methicillin-resistant coagulase-negative staphylococcus	2.0	2.0	0.5	2.0	0.5

MIC: minimum inhibitory concentration; Quin/dalfo: quinupristin/dalfopristin.

Table 6. Ceftobiprole in vitro activity against Enterobacteriaceae [30]

Organism	MIC_{90} (μg/mL)				
	Ceftobiprole	Cefepime	Pip/Tazo	Imipenem	Ciprofloxacin
Escherichia coli (*N* = 43)	0.06	⩽0.12	4.0	0.25	>2.0
Klebsiella pneumoniae (*N* = 30)	0.06	⩽0.12	16.0	0.5	⩽0.25
Enterobacter cloacae (*N* = 58)	0.12	0.25	4.0	0.5	⩽0.25
Indole-positive *Proteae* (*N* = 34)	>32.0	0.25	4.0	2.0	>2.0
Serratia spp. (*N* = 25)	8.0	0.5	64.0	1.0	2.0

MIC: minimum inhibitory concentration; Pip/Tazo: piperacillin/tazobactam.

Table 7. Ceftobiprole in vitro activity against Gram-negative bacteria with an extended-spectrum β-lactamase (ESBL) phenotype [30]

Organism	MIC_{90} (μg/mL)					
	Ceftobiprole	Cefepime	Ceftazidime	Ciprofloxacin	Pip/tazo	Imipenem
Escherichia coli (*N* = 23)	>32.0	>16.0	>32.0	>2.0	128.0	0.12
Klebsiella pneumoniae (*N* = 25)	>32.0	>16.0	>16.0	>2.0	>128.0	0.5

MIC: minimum inhibitory concentration; Pip/tazo: piperacillin/tazobactam.

Table 8. Ceftobiprole in vitro activity against of Gram-negative non-fermenters [31]

Organism	MIC_{90} (μg/mL)					
	Ceftobiprole	Cefepime	Ceftazidime	Ciprofloxacin	Ceftriaxone	Imipenem
Acinetobacter baumannii (*N* = 10)	16.0	32.0	64.0	0.25	64.0	0.5
Pseudomonas aeruginosa (*N* = 15)	32.0	16.0	8.0	2.0	>64.0	4.0

MIC: minimum inhibitory concentration.

pneumoniae, *Enterobacter cloacae*, indole-positive *Proteae*, *Serratia* spp, *A. baumannii*, and *P. aeruginosa*. [30,31] These findings suggest that ceftobiprole will have a significant role to play in the treatment of MRSA, drug-resistant streptococci, and other bacterial species. Tables 5 and 6 summarize the in vitro activity of ceftobiprole against selected Gram-positive staphylococci and species of Enterobacteriaceae. [29,30] Tables 7 and 8 present the in vitro activity of ceftobiprole against *E. coli* and *K. pneumoniae* isolates with an extended-spectrum β-lactamase (ESBL) phenotype as well as two Gram-negative non-fermenters. [30,31]

3.4. Iclaprim

Iclaprim is a selective dihydrofolate reductase inhibitor from a class of diaminopyrimidines that is currently in phase 3 trials. Iclaprim at concentrations close to the MIC has exhibited antimicrobial efficacy against Gram-positive pathogens including resistant *S. aureus* (MRSA, VISA, GISA), *S. pneumoniae*, enterococci, and several Gram-negative strains. The antibacterial profile of iclaprim compared with trimethoprim, vancomycin, linezolid, and erythromycin for the treatment of a variety of bacterial species is presented in Table 9. [32]

Table 9. In vitro activity of iclaprim against of Gram-positive and Gram-negative bacteria [32]

Organism	MIC_{90} (μg/mL)				
	Iclaprim	Trimetho-prim	Vanco-mycin	Line-zolid	Erythro-mycin
Staphylococcus aureus					
methicillin-sensitive	0.06	16.0	1.0	8.0	1.0
methicillin-resistant	0.06	8.0	1.0	8.0	10.0
Streptococcus pyogenes	0.03	64.0	1.0	2.0	32.0
S. agalactiae	0.5	128.0	0.5	2.0	8.0
S. pneumoniae (PRSP)	4.0	>128.0	1.0	2.0	32.0
Enterococcus spp.	0.12	8.0	2.0	4.0	32.0
Haemophilus influenzae	0.5	1.0	128.0	64.0	8.0
Moraxella catarrhalis	4.0	128.0	64.0	8.0	0.25

MIC: minimum inhibitory concentration; PRSP: penicillin-resistant.

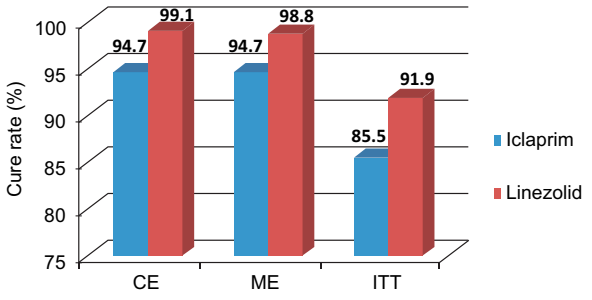

Fig. 1. Cure rates for iclaprim compared with linezolid for complicated skin and skin structure infections – ASSIST-1 results.[33] CE: clinically evaluable; ITT: intent-to-treat; ME: microbiologically evaluable.

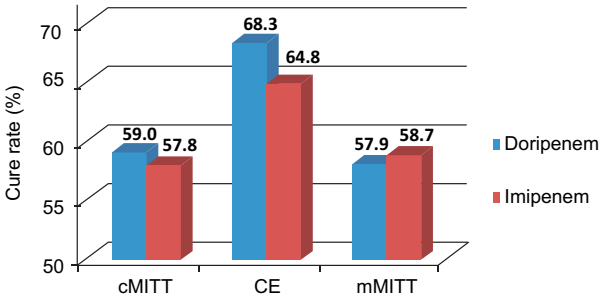

Fig. 2. Clinical cure rates for ventilator-assisted pneumonia: doripenem vs. imipenem.[38] CE: clinically evaluable; cMITT: clinical modified intent-to-treat; mMITT: microbiologically modified intent-to-treat.

A phase 3, randomized, double-blind, controlled trial enrolled 497 adult patients with skin and skin structure infections to evaluate the effects of iclaprim 0.8 mg/kg given by i.v. infusion twice daily, or linezolid 600 mg i.v. infusion daily for 10–14 d. The overall clinical cure rates in the intent-to-treat populations were 85.5% for iclaprim compared with 91.9% for linezolid, which confirmed the non-inferiority of iclaprim to linezolid (Fig. 1).[33]

3.5. New antimicrobials for MDR Gram-negative bacteria

Several antimicrobial agents exhibiting activity against MDR Gram-negative bacteria have been approved or are currently in development.[34] These include doripenem, faropenem, tebipenem (carbapenems), ceftobiprole and ceftaroline (cephalosporins), iclaprim (a diaminopyrimidine), garenoxacin, sitafloxacin, DW 286a (fluoroquinolones), and tigecycline (a broad-spectrum glycylcycline).

Doripenem, structurally related to penicillin, was approved by the FDA in 2007 for the treatment of complicated intra-abdominal infections and complicated urinary tract infections.[35] It is a new 1-β-methyl carbapenem with side-chain substitutions that enhance its activity against non-fermentative Gram-negative bacilli.[36,37] This agent is stable to human renal dehydropeptidases and is also stable in the presence of ESBLs. The pharmacokinetic properties of doripenem are similar to those of meropenem, with a 1 h half-life and 8.9% serum protein binding. Several recent trials suggest that doripenem offers the most favourable characteristics of antimicrobials of the carbapenem class, as it combines the excellent in vitro activity of imipenem against Gram-positive cocci with that of meropenem against Gram-negative bacteria.[37]

An international surveillance report completed in 2003 evaluated the spectrum of activity and potency of doripenem against 16,008 bacterial isolates. Results from this international analysis demonstrated that doripenem has the greatest activity (MIC_{90} 0.03–0.5 mg/L) against Gram-positive pathogens, especially oxacillin-susceptible staphylococci, *S. pneumoniae*, and β-haemolytic and viridans group streptococci.[37] A phase 3 prospective, multicenter, parallel group, randomized, active control, open-label trial enrolled 531 adults with ventilator-associated pneumonia. Patients were stratified by duration of ventilation support, severity of illness, Acute Physiology and Chronic Health Evaluation II score, and geographic region. They were then randomized to doripenem 500 mg q8h (4 h i.v. infusion), imipenem 500 mg q6h, or 1,000 mg q8h via 30 or 60 min intravenous infusion. Doripenem was clinically equivalent to the two imipenem regimens, with a clinical cure rate in evaluable patients of 68.3% for doripenem compared with 64.2% for the two imipenem regimens. Additional results by various subgroups of patients, including the microbiologically modified intent-to-treat and clinical modified intent-to-treat populations, are presented in Fig. 2. Doripenem was more effective for the treatment of infections caused by *E. coli*, *K. pneumoniae* and *P. aeruginosa* than other carbapenems with respect to clinical cure and microbiological cure rates. Doripenem showed much higher cure rates than other carbapenems against *P. aeruginosa* infections.[38] This agent has potential for broad use, including against previously carbapenem-resistant or intermediate isolates, including *P. aeruginosa*.[36,37]

4. Conclusions

Despite growing antimicrobial resistance in major bacterial pathogens, relatively few new antimicrobial options are available and effective against these resistant strains. The current pipeline of products is primarily focused on MRSA and Gram-positive cocci, although new peptides are in development with promising efficacy against Gram-negative bacteria. Specifically, new carbapenems, such as doripenem, appear to demonstrate more activity than other carbapenems against Gram-negative and non-fermenting bacteria. Additional data from clinical trials will be required to confirm these results. As clinicians await results from ongoing trials, they will be challenged to use currently available antimicrobial agents more appropriately to prevent the development of resistance.

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