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REVIEW

New and emerging treatment of *Staphylococcus aureus* infections in the hospital setting

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA), both hospital-acquired and community-acquired, is a dangerous pathogen that is involved in an increasing number of serious infections with high risk for morbidity and mortality. Community-acquired MRSA strains have epidemic potential and can be particularly virulent. Vancomycin has been the standard hospital treatment for the past 40 years, but vancomycin-resistant isolates of *S. aureus* have emerged in the USA, and vancomycin-intermediate isolates are increasingly being reported worldwide. New antimicrobial agents with activity against multidrug-resistant *S. aureus* and other resistant pathogens are urgently needed. Despite great strides, further advances in our understanding of the molecular and biochemical mechanisms responsible for antimicrobial resistance are still required. Several agents have been recently approved for the treatment of serious Gram-positive infections, including linezolid, daptomycin, and tigecycline. The novel investigational cephalosporin, ceftobiprole, is one of the first penicillinase-resistant agents to target penicillin-binding protein 2a (or PBP2a), an acquired PBP with low β-lactam-affinity that confers intrinsic β-lactam resistance to *S. aureus* and other staphylococci. This mechanism of PBP binding, including inhibition of PBP2a, confers broad-spectrum activity against clinically important Gram-negative and Gram-positive pathogens, including MRSA. Phase III clinical trials comparing ceftobiprole with vancomycin alone and in combination with ceftazidime for the treatment of complicated skin and skin structure infections showed ceftobiprole to have efficacy similar to the efficacy of these comparators as evidenced by non-inferior clinical cure and microbiological eradication rates.

Keywords Ceftobiprole, MRSA, PBP2a, resistance, review, SCC*mec*

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INTRODUCTION

Clinicians are faced with patients who have virulent, difficult-to-treat infections caused by antimicrobial-resistant pathogens on an increasingly frequent basis, in both the inpatient and outpatient settings. The extent of this challenge is shown by findings from the Surveillance Network-USA from 300 microbiology laboratories across the USA between 1998 and March 2005. From a total of over three million bacterial isolates from inpatients, *Staphylococcus aureus* was the most commonly observed species, with a prevalence of 18.8% [1]. Infection with *S. aureus* in hospitalised patients has been associated with a five-fold higher rate of in-hospital all-cause mortality, a three-fold longer length of stay, and a three-fold higher total hospital expenditure as compared with that for uninfected patients [2].

S. aureus has proven to be adept at developing resistance to antimicrobial agents. Methicillin resistance is only the most recent twist in the road towards β-lactam resistance that began decades ago. Strains of *S. aureus* resistant to semi-synthetic penicillins were already recognised as problematic within the first few years of the introduction of these agents [3,4].

The challenge of finding new chemotherapeutic agents to treat infections with antimicrobial-resistant *S. aureus* is not likely to abate. Methicillin-resistant *S. aureus* (MRSA) has become endemic in

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the USA and continues to grow in prevalence in Europe and other areas of the world [5]. Furthermore, the clinical usefulness of vancomycin is expected to diminish because of the emergence of vancomycin-resistant *S. aureus* (VRSA) and vancomycin-intermediate *S. aureus* (VISA) [6,7]. Antimicrobial resistance in *S. aureus* is responsible for the poor clinical outcomes associated with this pathogen; infection-attributable mortality is twice as great with MRSA as with methicillin-susceptible *S. aureus* (MSSA) [8].

The purpose of this article is to review the knowledge gained over the past several years with respect to mechanisms of resistance of *S. aureus* to β-lactams at the molecular, biochemical and structural biological levels. The article will also discuss targets for development of new anti-MRSA agents, with a focus on the novel cephalosporin ceftobiprole, a β-lactam with broad-spectrum activity that was designed to directly overcome the prevalent mechanism of methicillin resistance.

GENETIC ORIGIN OF METHICILLIN RESISTANCE

Methicillin resistance is associated with the acquisition of a particular resistance island called SCC*mec*, where SCC stands for staphylococcal cassette chromosome and *mec* for the genetic element conferring resistance to methicillin [9]. SCC*mec* is an exogenous piece of DNA that may vary between 15 and 60 kb and is absent from methicillin-susceptible staphylococci. Its boundaries are demarcated by direct and inverted repeats, which allow integration at a homologous site into the chromosome. Critical genes of SCC*mec* include the recombinases *ccr*A and *ccr*B, which can mediate mobilisation of the whole element, and the *mec*A gene, which mediates β-lactam resistance [10]. The *mec*A gene encodes for a particular penicillin-binding protein (PBP) called PBP2a, which has a very low affinity for methicillin and most other β-lactam drugs [11]. Hence, PBP2a is responsible for the intrinsic resistance of MRSA to almost all β-lactams (see below).

At least five types of SCC*mec* were discriminated on the basis of the structure of their *ccr*A–B and *mec*A complexes [10,12,13]. These five types are likely to mirror major original MRSA clones. SCC*mec* types I, II and III were shown to belong to hospital clones (Fig. 1) [14]. Types II and III harbour multiple resistance determinants, have relatively large sizes (35–60 kb), and are difficult to mobilise. Hence, they are stable. Recently, a fourth and a fifth type (type IV and type V, respectively) of SCC*mec* have been identified as being typical of community-acquired MRSA [13,15]. They are

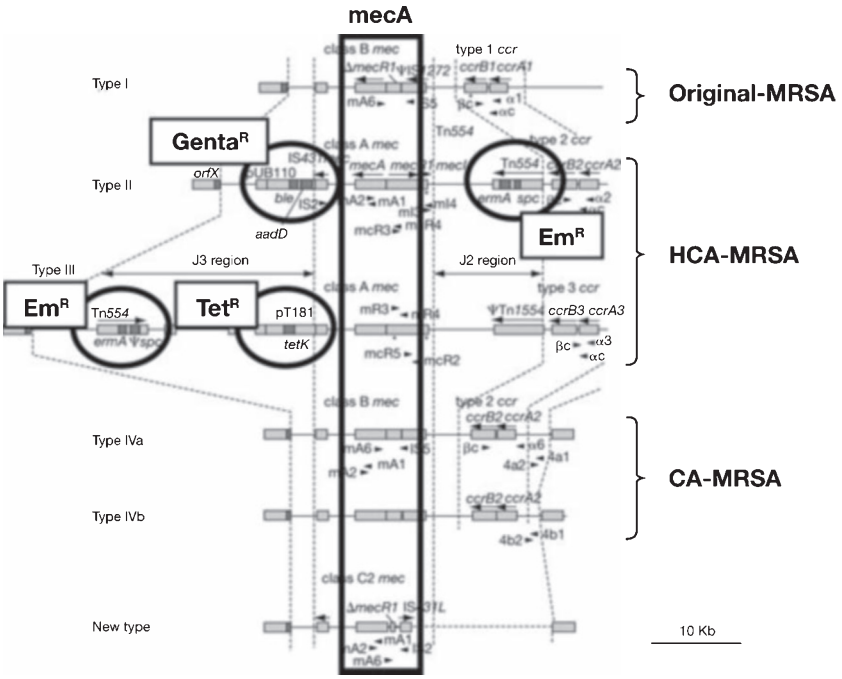

Fig. 1. Structures of staphylococcal cassette chromosome types based on multiple-locus sequence typing. Adapted with permission from Okuma *et al.* [14].

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much smaller (*c*. 15 kb) than their hospital-related congeners, do not carry multiple antibiotic resistance genes, and may be easier to mobilise (Fig. 1) [4,14]. The SCC*mec* types are often associated with other elements in the same bacterium, including the Panton–Valentine leukocidin toxin, which is encoded by a virus, and multiple staphylococcal exotoxin (*set*) genes, which are located on the *ν*Sa*β* pathogenicity island [16]. Together, these elements may render the organism particularly fit and virulent.

It is unlikely that these particular community-acquired MRSA strains have arisen from hospital MRSA strains that permeated the community. Instead, it is more probable that community-acquired MRSA strains have emerged independently, having acquired their SCC*mec* from coagulase-negative staphylococcal donors [17], and were able to evolve either because of the widespread use of *β*-lactams, or because it provides another, as yet undetermined, advantage to the bacterium. Thus, on the basis of the epidemiology of MRSA infection, it has become important to distinguish healthcare-associated MRSA strains, which are multiresistant and carry the large and more evolved versions of SCC*mec*, from the genuine community-acquired MRSA strains, which tend to be still susceptible to many commonly used antibiotics (e.g., trimethoprim–sulfamethoxazole) and carry the smaller and possibly original forms of SCC*mec* [18,19].

LIMITATIONS OF CURRENT ANTIMICROBIAL AGENTS

Although several other antimicrobial agents besides methicillin and vancomycin have been used to manage *S. aureus* infections, these agents all have limitations for treating infections when methicillin- or vancomycin-resistant *S. aureus* is involved [20]. Multiresistance in nosocomial MRSA strains and many strains of community-acquired MRSA renders fluoroquinolones, aminoglycosides, erythromycin, and clindamycin useless [21]. With the possible exception of clindamycin, these agents are also ineffective against VRSA and hetero-VISA. Other agents have limited activity against specific resistant strains of *S. aureus* and lack specific efficacy characteristics that are necessary for particular clinical indications. Rifampin, with in-vitro activity against MRSA, has minimal activity against VRSA and hetero-VISA, has been associated with rapid development of resistance, and is not recommended as monotherapy for invasive infections. Trimethoprim–sulfamethoxazole has activity against MRSA and VISA, but clinical data on efficacy in serious infections are lacking and/or difficult to interpret. Also, this agent is not recommended as empirical therapy for complicated skin and skin structure infections (cSSSIs) if group A streptococci are suspected. Tetracyclines, which have in-vitro activity against community-acquired MRSA, are effective for skin infections, but data on efficacy for invasive disease are lacking, and, like trimethoprim–sulfamethoxazole, tetracyclines are not recommended as empirical therapy if group A streptococci are suspected [20].

NEW NON-*β*-LACTAM DRUGS ACTIVE AGAINST MRSA

During the last few decades, drug discovery has not always kept up with the emergence of antimicrobial resistance and the increasing need for new agents with which to treat patients with serious bacterial infections [22]. The first antimicrobial drug classes were the sulphonamides, introduced in 1935, and the penicillins, introduced in 1941, and these were followed by three other antimicrobial drug classes (cephalosporins, aminoglycosides and chloranphenicol), which became available in the 1940s. Development of new antimicrobial drug classes reached a peak in the 1950s with the introduction of six new classes (tetracyclines, macrolides-lincosamides-streptogramins, glycopeptides, rifamycins and nitroimidazoles). Since then, successful research on and development of new antimicrobial classes has slowed, with only two new classes emerging in the 1960s (quinolones and trimethoprim), and then none until 2000, with the release of an oxazolidinone, followed by a lipopeptide in 2003. The state of antibiotic development is illustrated by a survey in 2002 of clinical development programmes. Although the total expenditure for antimicrobial drug development of the ten largest pharmaceutical companies has increased from $21.9 billion in 1998 to $28.8 billion in 2002, an increase of 31%, FDA approval of new antimicrobial agents has decreased by 56% over the last 20 years [23]. Likewise, the number of new antibacterial drugs approved each year by the FDA has decreased from 2.9 in the 1960s to 1.6 since

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2000 [24]. A number of reasons may explain this worrisome situation, including low commercial value of niche drugs that treat infections caused by resistant pathogens, and increasing constraints in designing appropriate clinical trials.

Despite the general paucity of research on and development of antimicrobials as compared with that for agents for other therapeutic areas, anti-MRSA agents have received priority within antimicrobial research. Many of these agents target bacterial protein synthesis, some are directed against the established target of peptidoglycan synthesis, and a few are aimed at new drug targets, including peptide deformylase. These are briefly summarised below.

Protein synthesis inhibitors

Oxazolidinones, macrolides–streptogramins–lincosamides (MLS_{AB}) and glycylcyclines are the major molecule classes in this group. The oxazolidinone linezolid is a narrow-spectrum anti-Gram-positive compound. It prevents formation of a 70S initiation complex by binding to the 50S ribosomal subunit near the interface with the 30S subunit [25]. This agent is bacteriostatic against staphylococci [25] and has an MIC_{90} of 2 mg/L against MRSA [26]. Linezolid is approved in the USA for the treatment of nosocomial pneumonia due to MSSA, MRSA, and multidrug-resistant *Streptococcus pneumoniae*, and cSSSIs (including diabetic foot infections) caused by MSSA, MRSA, *Streptococcus pyogenes*, or *Streptococcus agalactiae* [25]. The MLS_{AB} quinupristin (streptogramin B)–dalfopristin (streptogramin A) also targets primarily Gram-positive bacteria. Its two compounds bind synergistically to the 50S subunit of the bacterial ribosome, inhibiting protein synthesis during both the early (quinupristin) and late (dalfopristin) phases [27]. The drug combination has an MIC_{90} of 1 mg/L against MRSA and is bactericidal against MLS_B-susceptible isolates, but only bacteriostatic against constitutively MLS_B-resistant strains [26]. This combination agent is approved in the USA for the treatment of serious or life-threatening infections caused by *Enterococcus faecium* and for cSSSIs caused by MRSA [27]. The glycylcycline tigecycline is a modified tetracycline that has a broad spectrum of antibacterial activity. It inhibits protein synthesis by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome [28]. This agent is not affected by ribosomal protection or drug efflux (the two main tetracycline resistance mechanisms) [29]. Tigecycline is bacteriostatic against MRSA (MIC_{90} 0.5 mg/L), has in-vitro activity against VISA and VRSA (MIC_{90} ≤0.5 mg/L), and is approved in the USA for cSSSIs caused by MRSA, and in the European Union for cSSSIs and complicated intra-abdominal infections [28,30].

Transpeptidase/transglycosylase inhibitors

Two new glycopeptides, dalbavancin and telavancin, target transpeptidase and transglycosylase to inhibit peptidoglycan synthesis. Like other glycopeptides, they are active only against Gram-positive bacteria. The MIC_{90}s of these agents for MRSA are 0.125 mg/L (dalbavancin) and ≤1.0 mg/L (telavancin, oritavancin) [31–33]. At present, neither of these agents has marketing approval.

Plasma membrane integrity

The cyclic lipopeptide daptomycin acts by altering the membrane ion flux. It is bactericidal against Gram-positive bacteria. It inhibits bacterial DNA and RNA synthesis as well as protein and lipid biosynthesis [34]. Daptomycin has an MIC_{90} of 2 mg/L against MRSA [35]. Daptomycin is approved in the European Union for the treatment of cSSSIs, right-sided endocarditis due to *S. aureus*, and *S. aureus* bacteraemia associated with right-sided endocarditis or cSSSIs [36], and in the USA for MRSA and MSSA cSSSIs and bacteraemia, including right-sided endocarditis [34].

Peptide deformylase inhibitors

Two peptide deformylase inhibitors, LBM415 and BB-83698, have demonstrated bacteriostatic effects on MRSA *in vitro* (MIC_{90} 2 mg/L for LBM415 and 8 mg/L for BB-83698) [37–39]. Definitive clinical evaluation with these compounds is as yet unavailable.

THE RATIONALE FOR DEVELOPING β-LACTAMS WITH IMPROVED PBP2A AFFINITY

Intrinsic resistance of *S. aureus* to methicillin and most other β-lactams is conferred by 78-kDa PBP2a,

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which is the product of the *mec*A gene [15,39]. PBPs are membrane-bound enzymes with multiple enzymatic functions, including transpeptidase and transglycosylase activities necessary for bacterial cell-wall synthesis. The transpeptidase sites of wild-type PBPs bind β-lactams with high affinity, resulting in inactivation of the bacterial enzymatic activity and inhibition of cell-wall synthesis and cell growth. In contrast, PBP2a has a low affinity for β-lactam agents and remains active in the presence of these agents [40–43].

However, the survival benefit that PBP2a confers to *S. aureus* by imparting resistance to methicillin has some intrinsic drawbacks, providing opportunities for drug development. First, it was originally thought that PBP2a possessed both transpeptidase and transglycosylase activity and thus could carry out peptidoglycan assembly—which requires both transpeptidase and transglycosylase—independently of the *S. aureus* wild-type PBPs. However, it turns out that PBP2a has only transpeptidase activity and thus must cooperate with the transglycosylase domain of wild-type PBPs to assemble its cell wall (Fig. 2) [44]. Moreover, only one of the four wild-type PBPs of *S. aureus* possesses a transglycosylase domain (i.e., class A PBP2), whereas the others are pure transpeptidases (i.e., class B PBP1, PBP3, and PBP4) that might also compete to use PBP2 as a partner for transglycosylation. Thus, the activity of PBP2a might be affected by the interaction of other PBPs with wild-type PBP2.

Second, PBP2a can process only specific types of cell-wall precursors, those that carry a pentaglycine decoration attached to the position-3 lysine of their stem peptides [43]. The assembly of this pentaglycine relies on the coordinated activity of more than 40 auxiliary genes, including the *fem* (factor essential for resistance to methicillin) and *aux* (auxiliary) genes [45,46]. Mutations in such genes have been associated with decreased resistance to methicillin (Fig. 3). Serendipitous alterations in any of these many determinants will abrogate PBP2a activity.

Third, although the SCC*mec* elements carrying the *mec*A genes are quite variable, the *mec*A gene itself—and hence PBP2a—is highly conserved [10,12,13]. Taken together, these elements indicate that PBP2a-mediated β-lactam resistance is under strong biological constraints. This assumption is also supported by the difficulty in obtaining PBP2a mutants with further decreased β-lactam affinity when MRSA strains are exposed to β-lactams with improved PBP2a-binding ability, and thus improved anti-MRSA activity [47]. Hence, the constraint of the system and wide conservation of PBP2a among the studied isolates paradoxically make low-affinity PBP2a a highly suitable target for drug-induced blockage.

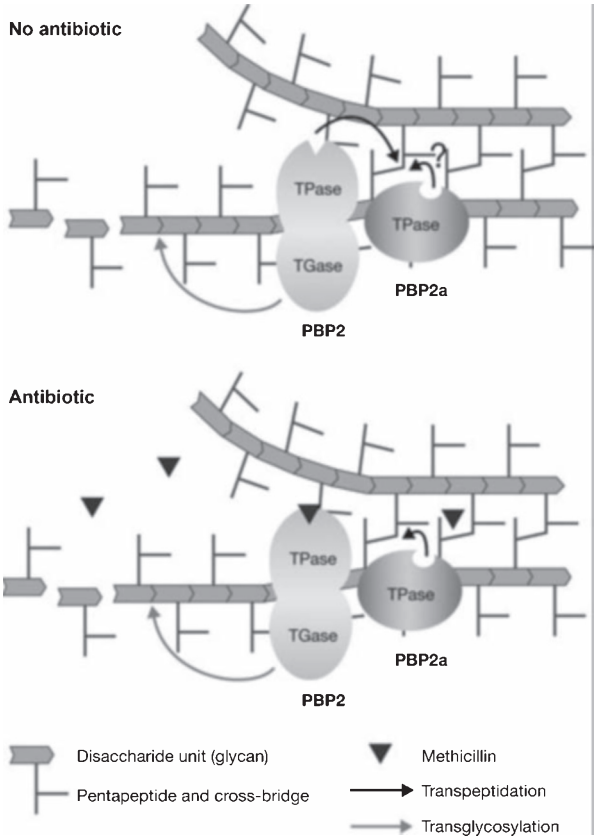

Fig. 2. Model for cooperative functioning between penicillin-binding protein (PBP)2a and wild-type PBP2 in methicillin-resistant *Staphylococcus aureus* (MRSA). Reprinted with permission from Pinho *et al.* [44]. In the absence of β-lactam antibiotics (top panel), wild-type PBP2 ensures both transpeptidase (TPase) and transglycosylase (TGase) activities to insert new peptidoglycan precursors into the walls. PBP2a is mostly inactive in this condition [43]. In the presence of β-lactams (lower panel), the TPase site of wild-type PBP2 becomes blocked, while that of low-affinity PBP2a remains free. Hence, PBP2a can complement the β-lactam-inhibited TPase of wild-type PBPs in the presence of antibiotics.

ANTI-MRSA AGENTS: MECHANISM-BASED INHIBITORS OF PBP2A

In theory, for a β-lactam agent to have activity against MRSA, it must target PBP2a and must not be vulnerable to hydrolysis by penicillinases.

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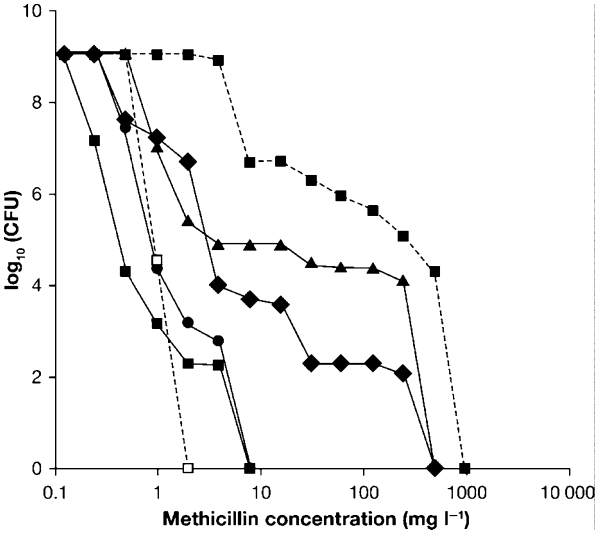

Fig. 3. The effects of mutations in *fem* genes on resistance to methicillin in *Staphylococcus aureus*. Reprinted with permission from Berger-Bachi [45]. Large bacterial populations (up to 10^9 CFU per plates; *y*-axis) were spread on nutrient agar plates containing increasing concentrations of methicillin (*x*-axis), and bacterial sub-populations growing on increased drug concentrations were determined. Open squares–dotted line, susceptible parent strain; filled squares–dotted line, heterogeneous MRSA; filled circles–solid line, inactivated *fem*A gene; filled squares–solid line, inactivated *fem*B gene; filled triangles–solid line, inactivated *fem*C gene; filled diamonds–solid line, inactivated *fem*D gene.

Findings from preclinical studies of experimental endocarditis provided support for this concept. First, older β-lactams such as penicillin G, ampicillin, amoxycillin and cefamandole were efficacious against infections caused by methicillin-resistant strains that did not produce penicillinase. Later, in the face of widespread penicillinase-based resistance, their efficacy was maintained by combining them with a penicillinase inhibitor [48–52]. Second, crystallography studies have confirmed interaction between the older β-lactam agents and the active site of PBP2a [53,54].

Despite these positive findings in preclinical studies, the strategy of using a combination of an older β-lactam plus a penicillinase inhibitor was not followed up with rigorous clinical studies, for at least two reasons. First, administration of large doses of the older molecules was needed, owing to their relatively high MICs for MRSA and difficult optimisation of the penicillinase-inhibiting dose (a necessary component, because most MRSA strains produce penicillinases). Second, glycopeptides were still uniformly active against MRSA at this time [55].

Instead, the design of penicillinase-resistant β-lactams with high affinity for PBP2a was pursued as a more promising approach. Investigational β-lactams with any activity against MRSA were mainly found in the carbapenem and cephem subclasses of cephalosporin β-lactams (reviewed in [55]). The first investigational anti-MRSA β-lactam to show clinical efficacy was ceftobiprole [56].

Ceftobiprole is a semi-synthetic molecule that varies from its cephem origin by alterations at the C-3 and C-7 components of the basic cephem ring (Fig. 4). These modifications increase its affinity for PBP2a through enhanced lipophilicity, and the substitution C-7 (an aminothiazolyhydroxyimino side chain) provides greater stability in the presence of penicillinases [55,57,58]. The solubility issues resulting from the increased lipophilicity of this compound were circumvented by synthesis of the water-soluble prodrug, ceftobiprole medocaril [58].

CEFTOBIPROLE

In-vitro activity

The in-vitro activity profile of ceftobiprole has been found to be consistent with that of the cephalosporin class, with bactericidal activity against many Gram-positive and Gram-negative species. In addition, ceftobiprole has been demonstrated to be bactericidal against MRSA [59].

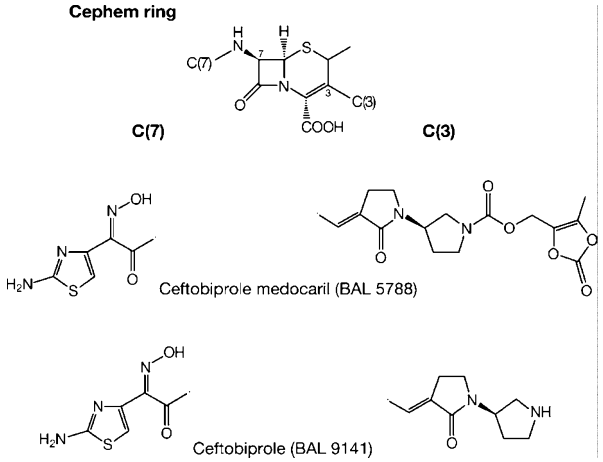

Fig. 4. Structures of the basic carbapenem ring, ceftobiprole medocaril, and ceftobiprole. Adapted with permission from Guignard *et al*. [55].

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Data from a study comparing ceftobiprole in-vitro activity against various Gram-positive and Gram-negative isolates indicated a broad spectrum of antimicrobial activity [26]. The MICs of ceftobiprole for clinically relevant Gram-positive and Gram-negative pathogens are listed in Table 1 [26,60]. Ceftobiprole, vancomycin and linezolid were the only highly effective agents against MRSA in this study (the other comparators included teicoplanin, quinupristin–dalfopristin, and ceftriaxone). The activity of ceftobiprole against coagulase-negative staphylococci was among the highest seen in this trial, with an inhibitory rate >90%; the other agents with this level of activity were vancomycin, linezolid, and quinupristin–dalfopristin [26].

The activity of ceftobiprole against *Enterococcus faecalis* was similar to that of ampicillin, penicillin, and amoxycillin–clavulanic acid. Although ceftobiprole activity against *E. faecium* was low, it was similar to that of the other tested penicillins against the remaining *Enterococcus* spp. [26].

Activity against *Streptococcus* spp. was particularly high for ceftobiprole, with high susceptibility seen for penicillin-resistant *S. pneumoniae*, penicillin-resistant viridans group streptococci, and β-haemolytic streptococci [26].

Surveillance studies have generally shown ceftobiprole to match broad-spectrum cephalosporins such as cefepime and ceftriaxone for potency against Gram-negative bacteria, but to be more active than these agents against Gram-positive organisms. The potency of ceftobiprole for inhibiting Gram-negative pathogens is species-dependent [60]. Although the in-vitro activity of this agent against Gram-negative pathogens overall does not reach that of imipenem and ciprofloxacin, its potency is greater than that of cefepime and cefozopran, and the latter two, along with ceftobiprole, have sufficient in-vitro activity to indicate clinical utility [58,60].

Clinical development

The efficacy of ceftobiprole has been assessed in clinical trials for treatment of cSSSIs. Two completed, randomised, double-blind, active-controlled, multicentre, multinational phase III clinical trials have been completed. The first trial demonstrated that ceftobiprole was non-inferior to the comparator vancomycin for clinical cure and clinical relapse rates in adult patients with cSSSIs due to Gram-positive pathogens (n = 784 for the intent-to-treat population). Non-inferiority of ceftobiprole was also seen in the analysis of overall microbiological eradication and microbiological relapse rates. Sub-analysis of patients with microbiologically confirmed involvement of *S. aureus* showed that clinical cure rates with ceftobiprole for MRSA and MSSA were similar to those for vancomycin and to the overall clinical cure rate [61].

The second phase III trial enrolled 828 adult patients with cSSSIs due to either Gram-positive or Gram-negative pathogens. Patients with diabetic foot infections were also included. The data demonstrated the non-inferiority of ceftobiprole monotherapy to vancomycin plus ceftazidime

Table 1. In-vitro antimicrobial activity of ceftobiprole against clinically important Gram-positive and Gram-negative pathogens

Species (number of isolates tested)	MIC (mg/L)			Reference
	50%	90%	Range	
Staphylococcus aureus, oxacillin-susceptible (50)	0.5	0.5	0.25–2	[26]
S. aureus, oxacillin-resistant (96)	1	2	0.12–2	[26]
Staphylococci, coagulase-negative, oxacillin-susceptible (26)	0.12	0.25	≤0.015–1	[26]
Staphylococci, coagulase-negative, oxacillin-resistant (90)	1	2	≤0.015–4	[26]
Enterococcus faecalis (62)	0.5	4	0.12–>32	[26]
Enterococcus faecium (51[a])	>32	>32	0.25–>32	[26]
Streptococcus pneumoniae, penicillin-resistant	0.25	0.25	≤0.015–1	[26]
β-Haemolytic streptococci (103)	≤0.015	≤0.015	≤0.015–0.06	[26]
Acinetobacter baumannii (10)	2	16	0.5–>64	[60]
P. aeruginosa (23)	2	8	0.12–16	[26]
P. aeruginosa (15)	8	32	0.25–64	[60]

[a]Included 25 vancomycin-resistant strains.

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combination therapy for clinical cure and clinical relapse rates. Non-inferiority of ceftobiprole to the combination comparator regimen was also shown for microbiological eradication and relapse rates. Sub-analysis of patients with microbiologically confirmed *S. aureus* infection showed that clinical cure rates with ceftobiprole for MRSA and MSSA were similar to those seen for vancomycin plus ceftazidime. Similarly, clinical cure rates for patients with confirmed involvement of *Pseudomonas aeruginosa* and other Gram-negative pathogens were comparable for patients receiving ceftobiprole and those receiving the combination comparator regimen [62].

Sub-analysis of findings for patients with diabetic foot infection, which are particularly difficult-to-treat cSSSIs because of deficiencies in host immunological responses and poor vascularisation [63], were comparable for patients receiving ceftobiprole and those receiving vancomycin plus ceftazidime (45th IDSA, abstract 1086).

Phase III clinical trials of ceftobiprole for the treatment of pneumonia have recently been completed, and data are expected to become available in 2008 (www.clinicaltrials.gov/ct2/results?term=ceftobiprole).

CONCLUSION

S. aureus is a major cause of life-threatening infections in hospital and community settings. The acquisition of genes encoding PBP2a has resulted in the emergence of MRSA, which is now a global health concern. Vancomycin has been the standard hospital treatment for the past 40 years, but clinical isolates of *S. aureus* with decreased susceptibility to vancomycin have been reported at healthcare institutions around the world. Strategies to develop new agents to overcome the challenge of MRSA have called upon our understanding of the mechanisms responsible for antimicrobial resistance. Several agents have been recently approved for the treatment of serious Gram-positive infections, including new protein synthesis inhibitors and a membrane-active lipopeptide. Agents in development include two glycopeptides that inhibit transpeptidase and transglycosylase, and novel investigational cephalosporins and carbapenems, including ceftobiprole, that target low-β-lactam-affinity PBP2a. Ceftobiprole has demonstrated a broad spectrum of activity against clinically important Gram-negative and Gram-positive pathogens, including MRSA. This spectrum of activity is wider than that of other cephalosporins such as cefepime and ceftriaxone. In phase III clinical trials, ceftobiprole was as effective as vancomycin for the treatment of Gram-positive cSSSIs, and as effective as the combination of vancomycin and ceftazidime for the treatment of Gram-positive and Gram-negative cSSSIs.

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REFERENCES

1. Styers D, Sheehan DJ, Hogan P, Sahm DF. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among *Staphylococcus aureus*: 2005 status in the United States. *Ann Clin Microbiol Antimicrob* 2006; **5:** 2.
2. Noskin GA, Rubin RJ, Schentag JJ *et al.* The burden of *Staphylococcus aureus* infections on hospitals in the United States: an analysis of the 2000 and 2001 Nationwide Inpatient Sample Database. *Arch Intern Med* 2005; **165:** 1756–1761.
3. Jevons MP. Celbenin-resistant staphylococci. *BMJ* 1961; **i:** 124–125.
4. Enright MC, Robinson DA, Randle G, Feil EJ, Grundmann H, Spratt BG. The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). *Proc Natl Acad Sci USA* 2002; **99:** 7687–7692.
5. Kluytmans-Vandenbergh MF, Kluytmans JA. Community-acquired methicillin-resistant *Staphylococcus aureus*: current perspectives. *Clin Microbiol Infect* 2006; **12** (suppl 1)**:** 9–15.
6. Appelbaum PC. The emergence of vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus*. *Clin Microbiol Infect* 2006; **12** (suppl 1)**:** 16–23.
7. Deresinski S. Counterpoint: vancomycin and *Staphylococcus aureus*—an antibiotic enters obsolescence. *Clin Infect Dis* 2007; **44:** 1543–1548.
8. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis* 2003; **36:** 1433–1437.
9. Katayama Y, Ito T, Hiramatsu K. A new class of genetic element, staphylococcus cassette chromosome mec, encodes methicillin resistance in *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2000; **44:** 1549–1555.
10. Ito T, Okuma K, Ma XX, Yuzawa H, Hiramatsu K. Insights on antibiotic resistance of *Staphylococcus aureus* from its whole genome: genomic island SCC. *Drug Resist Updat* 2003; **6:** 41–52.
11. Chambers HF, Hartman BJ, Tomasz A. Increased amounts of a novel penicillin-binding protein in a strain of methicillin-resistant *Staphylococcus aureus* exposed to nafcillin. *J Clin Invest* 1985; **76:** 325–331.

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12. Ito T, Katayama Y, Asada K *et al*. Structural comparison of three types of staphylococcal cassette chromosome *mec* integrated in the chromosome in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2001; **45:** 1323–1336.
13. Ma XX, Ito T, Tiensasitorn C *et al*. Novel type of staphylococcal cassette chromosome *mec* identified in community-acquired methicillin-resistant *Staphylococcus aureus* strains. *Antimicrob Agents Chemother* 2002; **46:** 1147–1152.
14. Okuma K, Iwakawa K, Turnidge JD *et al*. Dissemination of new methicillin-resistant *Staphylococcus aureus* clones in the community. *J Clin Microbiol* 2002; **40:** 4289–4294.
15. Ito T, Ma XX, Takeuchi F, Okuma K, Yuzawa H, Hiramatsu K. Novel type V staphylococcal cassette chromosome mec driven by a novel cassette chromosome recombinase, ccrC. *Antimicrob Agents Chemother* 2004; **48:** 2637–2651.
16. Baba T, Takeuchi F, Kuroda M *et al*. Genome and virulence determinants of high virulence community-acquired MRSA. *Lancet* 2002; **359:** 1819–1827.
17. Couto I, de Lencastre H, Severina E *et al*. Ubiquitous presence of a mecA homologue in natural isolates of *Staphylococcus sciuri*. *Microb Drug Resist* 1996; **2:** 377–391.
18. Shorr AF, Tabak YP, Killian AD, Gupta V, Liu LZ, Kollef MH. Healthcare-associated bloodstream infection: a distinct entity? Insights from a large U.S. database *Crit Care Med* 2006; **34:** 2588–2595.
19. Siegman-Igra Y, Fourer B, Orni-Wasserlauf R *et al*. Reappraisal of community-acquired bacteremia: a proposal of a new classification for the spectrum of acquisition of bacteremia. *Clin Infect Dis* 2002; **34:** 1431–1439.
20. Drew RH. Emerging options for treatment of invasive, multidrug-resistant *Staphylococcus aureus* infections. *Pharmacotherapy* 2007; **27:** 227–249.
21. Chavez-Bueno S, Bozdogan B, Katz K *et al*. Inducible clindamycin resistance and molecular epidemiologic trends of pediatric community-acquired methicillin-resistant *Staphylococcus aureus* in Dallas, Texas. *Antimicrob Agents Chemother* 2005; **49:** 2283–2288.
22. Infectious Diseases Society of America. *Bad bugs, no drugs*. 2004. http://www.idsociety.org/WorkArea/showcontent.aspx?id=5554
23. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. *Clin Infect Dis* 2004; **38:** 1279–1286.
24. Powers JH. Antimicrobial drug development—the past, the present, and the future. *Clin Microbiol Infect* 2004; **10** (suppl 4)**:** 23–31.
25. Food and Drug Administration, US Department of Health and Human Services. 2004. http://www.fda.gov/cder/drug/infopage/linezolid/default.htm
26. Jones RN, Deshpande LM, Mutnick AH, Biedenbach DJ. In vitro evaluation of BAL9141, a novel parenteral cephalosporin active against oxacillin-resistant staphylococci. *J Antimicrob Chemother* 2002; **50:** 915–932.
27. Food and Drug Administration, US Department of Health and Human Services. 2007. http://www.fda.gov/cder/consumerinfo/druginfo/synercid.htm
28. Chopra I. Glycylcyclines: Third generation tetracycline antibiotics. *Curr Opin Pharmacol* 2001; **1:** 464–469.
29. Doan TL, Fung HB, Mehta D, Riska PF. Tigecycline: a glycylcycline antimicrobial agent. *Clin Ther* 2006; **28:** 1079–1106.
30. European Medicines Agency (EMEA). *Tygacil. European Public Assessment Report*. 2006. http://www.emca.europa.eu/humandocs/Humans/EPAR/tygacil/tygacid.htm
31. Goldstein EJ, Citron DM, Warren YA, Tyrrell KL, Merriam CV, Fernandez HT. In vitro activities of dalbavancin and 12 other agents against 329 aerobic and anaerobic Gram-positive isolates recovered from diabetic foot infections. *Antimicrob Agents Chemother* 2006; **50:** 2875–2879.
32. Jones RN, Fritsche TR, Sader HS, Goldstein BP. Antimicrobial spectrum and potency of dalbavancin tested against clinical isolates from Europe and North America (2003): initial results from an international surveillance protocol. *J Chemother* 2005; **17:** 593–600.
33. Saravolatz LD, Pawlak J, Johnson LB. Comparative activity of telavancin against isolates of community-acquired methicillin-resistant *Staphylococcus aureus*. *J Antimicrob Chemother* 2007; **2007:** 406–409.
34. Cubist Pharmaceuticals, Inc. Cubicin IV. *Prescribing information*. 2007. http://www.cubicin.com/prescribe.pdf
35. Petersen PJ, Bradford PA, Weiss WJ, Murphy TM, Sum PE, Projan SJ. In vitro and in vivo activities of tigecycline (GAR-936), daptomycin, and comparative antimicrobial agents against glycopeptide-intermediate *Staphylococcus aureus* and other resistant Gram-positive pathogens. *Antimicrob Agents Chemother* 2002; **46:** 2595–2601.
36. European Medicines Agency (EMEA). Cubicin. *European Public Assessment Report*. 2006. http://www.emea.europa.eu/humandocs/Humans/EPAR/cubicin/cubicin.ht006D
37. Lofland D, Difuntorum S, Waller A *et al*. In vitro antibacterial activity of the peptide deformylase inhibitor BB-83698. *J Antimicrob Chemother* 2004; **53:** 664–668.
38. Fritsche TR, Sader HS, Cleeland R, Jones RN. Comparative antimicrobial characterization of LBM415 (NVP PDF-713), a new peptide deformylase inhibitor of clinical importance. *Antimicrob Agents Chemother* 2005; **49:** 1468–1476.
39. Lowy FD. Antimicrobial resistance: the example of *Staphylococcus aureus*. *J Clin Invest* 2003; **111:** 1265–1273.
40. Hartman BJ, Tomasz A. Low-affinity penicillin-binding protein associated with beta-lactam resistance in *Staphylococcus aureus*. *J Bacteriol* 1984; **158:** 513–516.
41. Utsui Y, Yokota T. Role of an altered penicillin-binding protein in methicillin- and cephem-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 1985; **28:** 397–403.
42. Song MD, Wachi M, Doi M, Ishino F, Matsuhashi M. Evolution of an inducible penicillin-target protein in methicillin-resistant *Staphylococcus aureus* by gene fusion. *FEBS Lett* 1987; **221:** 167–171.
43. de Jonge BL, Tomasz A. Abnormal peptidoglycan produced in a methicillin-resistant strain of *Staphylococcus aureus* grown in the presence of methicillin: functional role for penicillin-binding protein 2A in cell wall synthesis. *Antimicrob Agents Chemother* 1993; **37:** 342–346.
44. Pinho MG, de Lencastre H, Tomasz A. An acquired and a native penicillin-binding protein cooperate in building the cell wall of drug-resistant staphylococci. *Proc Natl Acad Sci USA* 2001; **98:** 10886–10891.
45. Berger-Bachi B. Expression of resistance to methicillin. *Trends Microbiol* 1994; **2:** 389–393.
46. de Lencastre H, de Jonge BL, Matthews PR, Tomasz A. Molecular aspects of methicillin resistance in *Staphylococcus aureus*. *J Antimicrob Chemother* 1994; **33:** 7–24.

© 2008 The Author

47. Katayama Y, Zhang HZ, Chambers HF. PBP 2a mutations producing very-high-level resistance to beta-lactams. *Antimicrob Agents Chemother* 2004; **48:** 453–459.
48. Moreillon P, Franciolli M, Cantoni L, Bille J, Glauser MP. Beta-lactam antibiotics active against methicillin-resistant *Staphylococcus aureus*. *J Infect Dis* 1991; **163:** 1165–1166.
49. Franciolli M, Bille J, Glauser MP, Moreillon P. Beta-lactam resistance mechanisms of methicillin-resistant *Staphylococcus aureus*. *J Infect Dis* 1991; **163:** 514–523.
50. Hirano L, Bayer AS. Beta-lactam–beta-lactamase-inhibitor combinations are active in experimental endocarditis caused by beta-lactamase-producing oxacillin-resistant staphylococci. *Antimicrob Agents Chemother* 1991; **35:** 685–690.
51. Chambers HF. In vitro and in vivo antistaphylococcal activities of L-695,256, a carbapenem with high affinity for the penicillin-binding protein PBP 2a. *Antimicrob Agents Chemother* 1995; **39:** 462–466.
52. Que YA, Entenza JM, Francioli P, Moreillon P. The impact of penicillinase on cefamandole treatment and prophylaxis of experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. *J Infect Dis* 1998; **177:** 146–154.
53. Lim D, Strynadka NC. Structural basis for the beta lactam resistance of PBP2a from methicillin-resistant *Staphylococcus aureus*. *Nat Struct Biol* 2002; **9:** 870–876.
54. Tomasz A. 'Intelligence coup' for drug designers: crystal structure of *Staphylococcus aureus* beta-lactam resistance protein PBP2A. *Lancet* 2003; **361:** 795–796.
55. Guignard B, Entenza JM, Moreillon P. Beta-lactams against methicillin-resistant *Staphylococcus aureus*. *Curr Opin Pharmacol* 2005; **5:** 479–489.
56. Bush K, Heep M, Macielag MJ, Noel GJ. Anti-MRSA beta-lactams in development, with a focus on ceftobiprole: the first anti-MRSA beta-lactam to demonstrate clinical efficacy. *Expert Opin Investig Drugs* 2007; **16:** 419–429.
57. Glinka TW. Novel cephalosporins for the treatment of MRSA infections. *Curr Opin Investig Drugs* 2002; **3:** 206–217.
58. Hebeisen P, Heinze-Krauss I, Angehrn P, Hohl P, Page MG, Then RL. In vitro and in vivo properties of Ro 63-9141, a novel broad-spectrum cephalosporin with activity against methicillin-resistant staphylococci. *Antimicrob Agents Chemother* 2001; **45:** 825–836.
59. Deshpande L, Rhomberg PR, Fritsche TR, Sader HS, Jones RN. Bactericidal activity of BAL9141, a novel parenteral cephalosporin against contemporary Gram-positive and Gram-negative isolates. *Diagn Microbiol Infect Dis* 2004; **50:** 73–75.
60. Zbinden R, Punter V, von Graevenitz A. In vitro activities of BAL9141, a novel broad-spectrum pyrrolidinone cephalosporin, against gram-negative nonfermenters. *Antimicrob Agents Chemother* 2002; **46:** 871–874.
61. Noel GJ, Strauss RS, Amsler K, Heep M, Pypstra R, Solomkin JS. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by Gram-positive bacteria. *Antimicrob Agents Chemother* 2008; **52:** 37–44.
62. Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS. A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. *Clin Infect Dis* 2008; **46:** 647–655.
63. Lipsky BA, Berendt AR, Deery HG *et al*. Diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2004; **39:** 885–910.

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