What's new in the treatment of serious MRSA infection?

Natasha E. Holmes[a] *and Benjamin P. Howden*[a,b,c]

Purpose of review
Vancomycin has been the cornerstone of treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) infections. This review describes new MRSA-active antibiotics that have recently been introduced and highlights emerging resistance.

Recent findings
Elevations in the vancomycin minimum inhibitory concentration within the susceptible range are associated with treatment failure and mortality in the treatment of MRSA infections. Ceftaroline and ceftobiprole are anti-MRSA cephalosporins and are noninferior to comparator agents in the treatment of acute bacterial skin and skin structure infections (ABSSSIs) and pneumonia. Tedizolid is more potent than linezolid, has improved pharmacokinetics and reduced toxicity and is active against *cfr*-containing *S. aureus*. Telavancin now has approval for treatment of hospital-acquired pneumonia, and recent phase 2 trial data showed similar cure rates in *S. aureus* bacteremia. Dalbavancin and oritavancin are administered once weekly and are noninferior to comparators for acute bacterial skin and skin structure infections. Resistance has emerged against many new anti-MRSA antimicrobials including ceftaroline. Combination therapy of β-lactams with vancomycin or daptomycin is increasing.

Summary
Several new MRSA-active agents are now approved for use, although much of the data is derived from treatment of acute bacterial skin and skin structure infections or pneumonia. Further studies are required for more invasive infections, such as bacteremia and endocarditis.

Keywords
antibiotic resistance, antibiotic treatment, lipoglycopeptide, methicillin-resistant *Staphylococcus aureus*, oxazolidinone

INTRODUCTION

Vancomycin has been the predominant treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) infections for decades; however, concerns about its efficacy have led to the increasing use of newer MRSA-active antimicrobials. The purpose of this review is to evaluate recent additions and changes to our armamentarium against MRSA since the last review published in 2011 [1]. Although a number of new agents have been investigated in clinical studies, these have been predominantly in skin and soft tissue infections and pneumonia, and not more invasive infections such as bacteremia and endocarditis.

CHANGING EPIDEMIOLOGY OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

A number of community-associated MRSA (CA-MRSA) clones have emerged in different geographic locations [2]. These include CC75 *S. argenteus* found in remote indigenous communities in Australia [3▪], ST72 in Korea [4▪], ST772 (the 'Bengal Bay' clone) initially found in South Asia but now reported elsewhere such as Australia [3▪–5▪], and ST80 that has spread from Europe to the Middle East [6]. Transmission between animals and humans has been

[a]Department of Infectious Diseases, Austin Centre for Infection Research, Austin Health, Heidelberg, [b]Department of Microbiology and Immunology, Microbiological Diagnostic Unit, University of Melbourne at The Peter Doherty Institute for Infection and Immunity, Parkville and [c]Department of Microbiology, Monash University, Clayton, Victoria, Australia

Correspondence to Professor Benjamin P. Howden, Microbiological Diagnostic Unit, University of Melbourne, Peter Doherty Institute for Infection and Immunity, First Floor, Building 248, The University of Melbourne, Parkville VIC 3010, Australia. Tel: +61 3 8344 5701; fax: +61 3 8344 7833; e-mail: bhowden@unimelb.edu.au

Curr Opin Infect Dis 2014, 27:471–478
DOI:10.1097/QCO.0000000000000101

KEY POINTS

- Ceftaroline and ceftobiprole are anti-MRSA cephalosporins approved for ABSSSI and pneumonia, and case reports have emerged of eosinophilic pneumonia associated with ceftaroline.
- Tedizolid offers once-daily oxazolidinone dosing with greater potency and reduced toxicity.
- Dalbavancin and oritavancin are lipoglycopeptides administered once weekly and may be convenient and cost-effective treatments for ABSSSI.
- β-Lactams may be combined with vancomycin or daptomycin to improve access to the cell wall or antibiotic binding in the treatment of MRSA infections.
- Resistance continues to emerge in anti-MRSA antimicrobials, although there are no data for new agents, such as tedizolid, dalbavancin and oritavancin.

demonstrated with livestock-associated *S. aureus* clones such as ST398 and ST291 [7–10]. There also is an animal reservoir for zoonotic transmission of the new *mecC* MRSA found predominantly in the Netherlands, Denmark and Belgium [11,12]. Recent modeling also suggests that CA-MRSA clones are displacing traditional hospital-associated MRSA clones within healthcare settings [2], although the burden of invasive MRSA infections has declined over the past decade [13,14▪].

VANCOMYCIN MINIMUM INHIBITORY CONCENTRATION AND HOW IT IMPACTS TREATMENT DECISIONS

Increased mortality and treatment failure have been observed in vancomycin-susceptible *S. aureus* infections in which the vancomycin minimum inhibitory concentration (MIC) is elevated within the susceptible range [15,16]. Newer antimicrobial compounds have not demonstrated superiority over vancomycin in primary outcomes during clinical trials, and there are issues of emerging cross-resistance among some new agents, particularly with previous vancomycin exposure. Recommendations outlined in the Infectious Diseases Society of America clinical practice guidelines for MRSA infections [17] remain valid: switch to alternative agents if there is no clinical or microbiologic response to vancomycin despite adequate source control regardless of the vancomycin MIC. However, vancomycin may be continued if there has been clinical and microbiologic improvement. A meta-analysis by van Hal *et al.* [15] concluded that there are no robust clinical trial data to support better survival rates with alternative antibiotics in high vancomycin MIC infection. Elevated vancomycin MIC has been reported in methicillin-susceptible *S. aureus* infections in which vancomycin therapy was not used [18,19], and increased mortality and treatment failure may relate to underlying organism factors such as genotype or virulence determinants [20] rather than direct therapeutic failure of vancomycin.

NEWER AGENTS WITH METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* ACTIVITY

Fortunately there have been several new antimicrobials approved or in development that have activity against multiresistant Gram-positive pathogens including MRSA.

Ceftaroline

Ceftaroline is a cephalosporin with activity against MRSA because of its affinity for penicillin-binding protein 2a (PBP2a) and has been approved for use in acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired pneumonia (CAP) [21,22]. The FOCUS 1 and 2 licensing studies for CAP specifically excluded patients with risk factors for MRSA pneumonia [23]. Clinical use in MRSA pneumonia and other invasive infections, such as bacteremia and endocarditis, is supported by case series [24▪,25,26,27▪,28,29] but not randomized controlled trial data. Results are eagerly anticipated from a multicenter randomized controlled trial of ceftaroline versus ceftriaxone plus vancomycin in patients with community-acquired bacterial pneumonia at risk of MRSA infection completed in December 2013 (ClinicalTrials.gov NCT01645735), and a multicenter open-label cohort study evaluating the safety and efficacy of ceftaroline in *S. aureus* bacteremia (including MRSA) is scheduled for completion in July 2014 (ClinicalTrials.gov NCT01701219).

Ceftaroline retains excellent activity against methicillin-susceptible *S. aureus* and MRSA in surveillance specimens collected for the AWARE program [30,31]. It is also active *in vitro* against heterogeneous vancomycin-intermediate *S. aureus* (hVISA), VISA and daptomycin nonsusceptible (DNS) *S. aureus* [32,33], including in endocarditis models, and enhances membrane binding and daptomycin activity in a pharmacokinetic/pharmacodynamic model of DNS VISA [34]. Although adverse effects were infrequent and rates of discontinuation in clinical trials were similar to comparator agents [23,35▪], off-label use has been associated with similar [27▪] or increased rates of hematologic

toxicities and rash leading to discontinuation [36]. Case reports of eosinophilic pneumonia when receiving ceftaroline for MRSA pneumonia have also been reported in postmarketing surveillance [29,37,38].

Ceftobiprole

Another anti-MRSA cephalosporin is ceftobiprole. In a randomized controlled trial of patients requiring hospitalization for CAP, it was noninferior to ceftriaxone with or without linezolid [39]. Ceftobiprole was also noninferior to ceftazidime plus linezolid in the treatment of hospital-acquired pneumonia (HAP) but not ventilator-associated pneumonia (VAP) [40▪]. Favorable rates of clinical cure and microbiologic eradication were observed in those patients with MRSA pneumonia. In a post-hoc pharmacokinetic/pharmacodynamic model there was a strong correlation between ceftobiprole exposure and improved clinical cure and microbiologic eradication [41]. It gained regulatory approval in October 2013 in 12 European countries for treatment of CAP and HAP but not VAP [42–44].

Tedizolid

A new addition to the oxazolidinone class is tedizolid (formerly known as torezolid). Improved pharmacokinetics facilitate once-daily dosing, and its in-vitro potency is up to 16 times that of linezolid [45▪▪,46▪▪]. It has been specifically designed to be active against linezolid-nonsusceptible (LNS) *S. aureus*, including strains containing the multidrug resistance *cfr* gene [45▪▪,47,48]. As with linezolid, tedizolid inhibits protein synthesis by binding to the 50S ribosomal subunit [45▪▪]. Although it has in-vitro activity against MRSA, there are fewer data on its efficacy against hVISA/VISA and vancomycin-resistant *S. aureus* (VRSA) [46▪▪,49,50]. In a phase 3 randomized controlled study (the ESTABLISH-1 trial), oral tedizolid 200 mg once-daily for 6 days was noninferior to oral linezolid 600 mg twice-daily for 10 days for ABSSSI [51▪▪], and oral and intravenous formulations were licensed in the United States in June 2014 after undergoing a priority review. As of July 2014, it is currently under evaluation in Europe [52]. Apart from the improved barrier to resistance and in-vitro efficacy, tedizolid also has less myelotoxicity and gastrointestinal disturbance [47,53▪▪]. Animal studies have also demonstrated a lack of serotonergic stimulation compared with linezolid due to a lack of monoamine oxidase inhibition at clinically relevant doses [53▪▪].

Telavancin

The lipoglycopeptides are semi-synthetic derivatives of glycopeptides. Telavancin is potently bactericidal due to dual mechanisms of action with inhibition of cell wall synthesis and cell membrane depolarization [54]. It has in-vitro activity against MRSA, VISA, DNS and LNS *S. aureus* [35▪,46▪▪]. Telavancin was approved in Europe and the United States for HAP caused by Gram-positive pathogens including MRSA in which alternative treatments are not suitable, on the basis of the results of the ATTAIN studies [55]. Of note, comparable cure rates were noted in patients with MRSA HAP. A post-hoc analysis of these studies demonstrated lower survival in telavancin-treated patients with moderate-to-severe renal insufficiency (creatinine clearance $<$50 ml/min) [56].

The ASSURE study (NCT00062647) was a phase 2 trial of telavancin compared with vancomycin or an antistaphylococcal penicillin for the treatment of uncomplicated *S. aureus* bacteremia, and this demonstrated similar cure rates between both groups [57▪▪]. Adverse events were more frequent in the telavancin group – particularly increases in serum creatinine – although drug discontinuation rates were similar in both treatment groups [57▪▪]. Adverse effects include QT prolongation [57▪▪,58] and elevations in serum creatinine and thrombocytopenia [55,58].

Dalbavancin

Dalbavancin is a teicoplanin-derived lipoglycopeptide with a prolonged half-life up to 8.5 days that facilitates once-weekly dosing [46▪▪,59▪▪]. In-vitro data demonstrate eight-fold to 16-fold more activity compared with vancomycin and daptomycin for clinically relevant multidrug-resistant Gram positive pathogens including MRSA [60], with a typical MIC range from 0.03 to 0.12 mg/l or less for *S. aureus* [60,61]. Dalbavancin is also active against hVISA, VISA and clinical staphylococcal strains from patients with osteomyelitis [61].

Although dalbavancin has not been studied in invasive infection, the DISCOVER 1 and 2 studies compared dalbavancin on days 1 and 8 with vancomycin for a minimum of 3 days plus a step-down to oral linezolid to complete 10–14 days of treatment for ABSSSI [62▪▪]. These studies enrolled patients with more severe ABSSSI, using the new criteria required by the United States Food and Drug Administration (FDA), and dalbavancin was noninferior to the comparator arm, including the subset of patients with MRSA [62▪▪]. Dalbavancin was recently approved by the FDA for the treatment of ABSSSI. Adverse effects were less frequent with dalbavancin and included gastrointestinal upset and pruritus.

Oritavancin

Oritavancin, like telavancin, is a lipoglycopeptide with a vancomycin-backbone. It had previously been sidelined from regulatory approval because of the requirement for further clinical studies. There has been confusion about the most appropriate dosing strategy, with doses in preclinical studies ranging from 200 to 1200 mg [46▪▪]. This was exacerbated by the discovery that oritavancin MICs against staphylococci and enterococci had been significantly underestimated because of oritavancin sticking to plastic tubes and microdilution wells (which can be overcome by including 0.002% polysorbate 80) [63]. It has a prolonged terminal half-life up to 393 h and has extensive tissue distribution [64,65]. MICs are two to eight-fold lower than vancomycin [66▪▪,67], with an MIC_{90} of 0.12 mg/l for multidrug-resistant *S. aureus* isolates collected in an international surveillance study [67]. Oritavancin also has activity against hVISA, VISA and VRSA strains [66▪▪,68] and *mecC* MRSA [69].

Results from SOLO 1, an international randomized double-blind study evaluating a single dose of oritavancin compared with vancomycin for the treatment of ABSSSI, were recently published [70▪▪]. Oritavancin was noninferior to vancomycin for the primary composite endpoint of early clinical evaluation at 48–72 h after initiation of study treatment, and also in the subset of patients with MRSA-proven infections. The frequency of adverse effects was similar [70▪▪]. Oritavancin was recently approved by the FDA for treatment of ABSSSI caused by certain susceptible pathogens, including MRSA, and regulatory approval is currently under review in Europe. There are no clinical trials registered for treatment of serious invasive infections; however, in-vitro data support its use in endocarditis and bacteremia, particularly as oritavancin has excellent intracellular bactericidal activity [64].

EMERGING RESISTANCE

Despite the lure of newer antimicrobials, *S. aureus* continues to develop reduced susceptibility or resistance to these agents. There are no current reports of resistance to lipoglycopeptides.

Vancomycin

Fortunately, VRSA remains relatively rare; however, there have been recent cases reported from India, Pakistan, Iran, Portugal and Brazil [71–74]. Most VRSA is due to the acquisition of the *vanA* resistance operon [75] that confers vancomycin resistance in enterococci. Worryingly, there is now a case report of a VRSA isolate with coexistent resistance to linezolid and streptogramins in the nasal cavity of a healthcare worker in Iran [72].

Teicoplanin

As with vancomycin, higher teicoplanin MICs have now also been associated with poor clinical outcomes in serious MRSA infections such as bacteremia and pneumonia [76,77].

Linezolid

Rates of linezolid resistance have remained relatively low and stable over the past 14 years as demonstrated by the ZAAPS and LEADER surveillance programs [78–80]. The most frequent cause of resistance involves mutations in the bacterial 23S ribosomal subunit, the binding site for linezolid [78–80]. Mutations in the 50S L3 and L4 ribosomal proteins have also been described. A plasmid-mediated acquisition of the *cfr* gene confers a multidrug-resistant phenotype to phenicols, lincosamides, oxazolidinones, pleuromutilins and streptogramin A (also known as the $PhLOPS_A$ phenotype), including in the USA300 community-associated MRSA clone [81].

Daptomycin

Genetic changes associated with the development of daptomycin resistance [82▪▪] can occur during treatment in patients with deep-seated or high bacterial burden infections [83], especially in the *mprF* gene resulting in altered cell membrane charge and daptomycin binding [82▪▪,84,85▪]. Recommended dosing of daptomycin for bacteremia and endocarditis now exceeds the initial FDA-approved dose of 6 mg/kg [17,86]. Coresistance to vancomycin and daptomycin can result from mutations in *walKR* and *rpoB*, and these mutations can arise during vancomycin treatment failure without daptomycin exposure [82▪▪,87–89]. Other changes targeting teichoic acids, phospholipid genes and cell surface charge have been implicated [90]. Interestingly, daptomycin nonsusceptibility was found in hVISA and VISA isolates collected before the introduction of daptomycin in Australia [91], further demonstrating that nonsusceptibility can emerge even without daptomycin selection pressure.

Ceftaroline

Heteroresistance to ceftaroline has been reported in laboratory isolates of MRSA, hVISA, VISA, DNS and LNS *S. aureus* [92]. Mutations in PBP2a lead to lower

binding affinity, reduced efficacy and higher MICs [93,94]. A study from Australia has demonstrated ceftaroline nonsusceptibility among multidrug-resistant MRSA clinical isolates, particularly in ST239 MRSA (an endemic hospital MRSA clone) [95].

Rifampicin

Although rifampicin is not a new MRSA-active agent, nor is rifampicin resistance a new phenomenon, it is important to appreciate that single mutations in the *rpoB* gene, which are commonly encountered in rifampicin-resistant *S. aureus*, can confer reduced susceptibility to both vancomycin and daptomycin [96,97]. Mutations in *rpoB* have also been associated with reduced susceptibility to host antimicrobial peptides and promote persistent infection [97]. Using dual therapy with vancomycin or daptomycin plus rifampicin without additional anti-MRSA agents is not recommended.

COMBINATION THERAPY

Combinations of vancomycin or daptomycin with β-lactams are being increasingly used to treat serious and invasive MRSA infections. Many in-vitro studies have demonstrated synergy with these combinations, even if the β-lactam itself does not possess anti-MRSA activity [46▪▪]. The proposed mechanism is the 'seesaw effect', in which β-lactams thin the cell wall to allow vancomycin to bind to target sites during cell wall synthesis, or in which β-lactams increase the negative cell surface charge to allow improved daptomycin binding and bactericidal activity [98▪▪]. Recent laboratory and animal studies have also demonstrated an impact of β-lactams on susceptibility to host immune factors [99▪▪]. Further studies to systematically evaluate the impact of combination therapy are warranted.

OTHER MANAGEMENT STRATEGIES

Much interest has been placed on the development of a staphylococcal vaccine as an infection prevention strategy. Unfortunately, despite promising in-vitro and early clinical studies, vaccine candidates have not been successful in phase 3 clinical trials [100,101]. The most recent trial of the *isdB*-containing V710 vaccine in patients undergoing cardiothoracic surgery did not show a reduction in *S. aureus* bacteremia and/or deep sternal wound infections, and was surprisingly associated with increased mortality [102▪▪]. Further analysis is under way to explain these findings.

The advent of benchtop next-generation sequencing techniques has allowed more efficient tracking of bacterial isolates in real time, for example, during a clinical outbreak of MRSA in a neonatal unit [103]. Apart from identifying potential transmission pathways or detecting antimicrobial resistance, this approach may also guide empiric therapy during an outbreak on the basis of the *in silico* antibiogram of identified strains.

CONCLUSION

A number of new antimicrobials active against Gram-positive pathogens, particularly MRSA, are available. These new drugs provide alternatives to vancomycin when there are concerns about clinical failure, and several are attractive options that involve less toxicity, requirement for therapeutic drug monitoring and fewer nursing procedures. Each new antibiotic is tempered by the development of antimicrobial resistance, so judicious use of existing and new agents is required to ensure longevity of these treatment options for serious invasive MRSA infections. Further clinical trials are warranted to investigate the benefits of combination therapy, and to evaluate these new antimicrobials in the treatment of invasive MRSA infection such as bacteremia or endocarditis.

Acknowledgements

N.E.H. is supported by a National Health and Medical Research Council Early Career Fellowship (APP1073378). B.P.H. is supported by a National Health and Medical Research Council Career Development Fellowship (APP1023526).

Conflicts of interest

The authors have no conflicts of interest to declare.

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