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Review

Vancomycin in the treatment of meticillin-resistant *Staphylococcus aureus* (MRSA) infection: End of an era?

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ABSTRACT

Infection with meticillin-resistant *Staphylococcus aureus* (MRSA) continues to have significant morbidity and mortality. Vancomycin, which has been the mainstay of treatment of invasive MRSA infections, has several drawbacks related to its pharmacological properties as well as varying degrees of emerging resistance. These resistant subpopulations are difficult to detect, making therapy with vancomycin less reliable. The newer agents such as linezolid, daptomycin, ceftaroline, and the newer glycopeptides telavancin and oritavancin are useful alternatives that could potentially replace vancomycin in the treatment of certain conditions. By summarising the discussions that took place at the III MRSA Consensus Conference in relation to the current place of vancomycin in therapy and the potential of the newer agents to replace vancomycin, this review focuses on the challenges faced by the laboratory and by clinicians in the diagnosis and treatment of MRSA infections.

Contents

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1. Introduction

Meticillin-resistant *Staphylococcus aureus* (MRSA) remains a key pathogen both in community and hospital settings. Despite the availability of antimicrobial agents such as vancomycin and teicoplanin, and more recently linezolid and daptomycin, both morbidity and mortality from MRSA infections remain substantial [1,2]. The previous expert consensus conference, which took place in Florence, Italy, published a paper in 2012 [3]. This review is a summary of the discussions that took place at the International Society of Chemotherapy MRSA panel meeting held in Naples in March 2012.

The last few years have seen a surge in the availability of antimicrobial agents active against MRSA, e.g. linezolid, daptomycin, tigecycline, telavancin and ceftaroline. However, the spread of resistance determinants among MRSA has continued. Fortunately, there are still only a small number of reports of fully vancomycin-resistant MRSA. The spread of MRSA has been reduced in many areas of the world (e.g. the UK, USA), but serious MRSA infections often still result in poor outcomes [4]. Thus, there is a continuing need to develop newer, more effective antimicrobial agents and to explore strategies that may enhance the potency of existing agents. This may include pharmacokinetic/pharmacodynamic (PK/PD) modelling studies, the use of combination therapy, and revisiting the current breakpoints. Antimicrobial susceptibility testing and the use of genotypic tests for resistance gene detection need to be standardised and must include all appropriate resistance gene alleles (e.g. *mecA* and *mecC*). Bovine and human strains of MRSA isolated in Denmark and the UK were reported to carry a novel *mecA* homologue (originally published as LGA251 but now renamed *mecC*) in a novel type XI staphylococcal cassette chromosome. This allele was present in ca. 70% of *mecA*-negative MRSA isolates [5]. How widely this gene will spread still has to be determined. Further complicating antimicrobial susceptibility testing are reports of *mecA*-positive invasive isolates of *S. aureus* that appear to be susceptible to oxacillin by phenotypic testing [6]. Reasons for such discrepancies may include inducible oxacillin resistance and heteroresistance, or a non-functional *mecA* determinant owing to mutation. Such discrepancies may be rare but, given the large denominator of MRSA infections, their impact on clinical management could be significant.

2. Place of vancomycin in the treatment of MRSA

S. aureus has evolved from susceptibility to virtually all antimicrobial agents, including penicillin, to multidrug resistance, including resistance to the newer agents daptomycin and linezolid. This includes varying degrees of resistance, such as vancomycin-intermediate *S. aureus* (VISA) and heteroresistant VISA (hVISA), that are a challenge both to laboratory detection and to clinical care. It is likely that the emergence of VISA from vancomycin-susceptible MRSA is a multistep process. VISA emerges from hVISA, a term that is not formally defined [7]. These phenotypic changes are orchestrated at the genetic level through a series of events [8].

A paper by Cafiso et al. underlines the complex genetic mechanisms that occur in the transition of vancomycin-susceptible MRSA to hVISA and VISA [9]. One mechanism of reduced susceptibility in VISA strains is a thickened cell wall. This is the end result of a process that is achieved either by producing excess cell wall precursors, by reduction in autolysis, or both [10]. The genetic mechanisms that underlie these alterations include loss of *agr* functions (the *agr* locus contains the *hld* gene encoding the δ-haemolysin) and alterations in *atl*, *lytM* and *sceD*, among others. Phenotypic changes include a high rate of cell wall turnover (enhanced expression of *sceD*) and a change to a positive surface charge (*mprF* upregulation). They result in reduced surface binding of antimicrobial agents such as vancomycin and daptomycin. Further changes to the regulatory mechanisms that control cell wall autolysis (i.e. downregulation of *atl* and *lytM*) give rise to cells with the VISA phenotype. Moreover, antimicrobial agents can induce these responses. For example, daptomycin leads to upregulation of the *mprF* gene leading to its exclusion from the cell by the increase in cell wall positive charges. Daptomycin-resistant mutants additionally demonstrate increased expression of the *dlt* operon, which increases the net surface charge on the cell. Acquisition of a positive surface charge in daptomycin-resistant cells is a dynamic process due to several mechanisms that operate in opposite directions. Mishra et al. hypothesised that the initial negative charge is a result of glutamate amidation on the cell surface, which leads to rapid entrapment of positively charged daptomycin molecules, followed by the overexpression of *mprF* (perhaps as a result of daptomycin-mediated induction) leading to acquisition of positive charges on the surface [11].

Whatever the genetic mechanisms, the ultimate biological outcome is reduced in vitro susceptibility to vancomycin. The extent to which these changes result in clinically relevant levels of resistance is uncertain, although cumulative data and opinion suggest that the utility of vancomycin in clinical practice may be limited as a result of these evolutionary changes. Thus, in an observational study of 1994 episodes of bacteraemia due to either MRSA or meticillin-susceptible *S. aureus* (MSSA), treatment with a glycopeptide was an independent predictor of higher mortality irrespective of meticillin resistance [12]. However, a substudy of 532 episodes found that mortality was significantly higher if the vancomycin E-test minimum inhibitory concentration (MIC) of the causal isolate was >1.5 μg/mL regardless of whether treatment was with vancomycin or flucloxacillin [13]. The latter finding suggests that the complex changes associated with the VISA and hVISA phenotypes have an influence on the course of infection quite apart from the efficacy of glycopeptides.

Evidence for a reduction in vancomycin efficacy against MRSA strains for which the vancomycin MIC is ≥2 μg/mL is accumulating; hence, the potential of clinical failure of vancomycin for treating infections caused by such strains should be considered. Risk factors for infection caused by MRSA strains with higher vancomycin MICs include exposure to vancomycin in the month prior to infection, recent hospitalisation or surgery, and bacteraemia prior to admission to an intensive care unit (ICU) [14,15]. Overcoming high vancomycin MICs by targeting higher trough levels has not been successful. In a prospective cohort study, Hidayat et al. reported that despite achieving the target trough level of at least four times the vancomycin MIC of the infecting isolate, patients in the high (≥2 μg/mL) vancomycin MIC group had significantly lower end-of-treatment responses (62% vs. 85%; $P = 0.02$) and a numerically higher mortality (24% vs. 10%; $P = 0.16$) compared with patients in the low (<2 μg/mL) vancomycin MIC group, with high vancomycin MIC being an independent predictor of poor outcome [16].

The global emergence of strains of *S. aureus* with reduced susceptibility to vancomycin within what is considered the susceptible range is widely acknowledged. However, there is debate about whether there has been a gradual increase in the MICs of vancomycin against *S. aureus* strains, i.e. 'MIC creep'. The phenomenon of vancomycin MIC creep, mostly in the susceptible range, was first observed in the last decade, with several independent studies reported increasing MICs in *S. aureus* strains over a variable period of time [17–20]. However, other centres found no evidence of MIC creep [21,22] or evidence of reduction in MICs over time [15]. Alós et al. demonstrated that such MIC changes were not observed in areas of low vancomycin use [23]. Kehrmann et al. suggested that the phenomenon was regional [24], whilst storage may result in reduced MICs, thus calling into

question the interpretation of studies including stored isolates [25,26]. Finally, the ideal laboratory method for detection of hVISA, which is conceivably responsible for even higher rates of failure of vancomycin therapy, has yet to be established. van Hal et al. compared the macromethod E-test (MET), the glycopeptide resistance detection (GRD) E-test, the standard vancomycin E-test, vancomycin broth microdilution (BMD) and VITEK® 2 testing using population analysis profiling utilising the area under the concentration–time curve (PAP-AUC) as the standard. The sensitivities and specificities of MET, GRD E-test, BMD (with an MIC cut-off ≥2 μg/mL) and standard vancomycin E-test (also with an MIC cut-off ≥2 μg/mL) were 89% and 55%, 71% and 94%, 82% and 97%, and 71% and 94% respectively. The most cost-effective strategy was BMD singly or in combination with PAP-AUC [27]. On the other hand, there are practical difficulties in carrying our PAP-AUC on a routine basis, and screening of isolates on brain–heart infusion agar containing teicoplanin 5 μg/mL followed by MET has been successfully used for determining the prevalence of hVISA [28]. As is true for any other test, the sensitivity and specificity depend upon the prevalence of hVISA. Although no methodology is perfect, it could be argued that the likelihood of hVISA is greater when the vancomycin MIC is ≥2 μg/mL by E-test, and lesser if the MIC is lower, e.g. ≤0.5 μg/mL [29].

Loss of the δ-haemolysin, referred to earlier as a potential genetic marker for hVISA detection, and the diagnostic utility of this phenomenon has been evaluated recently. Cafiso et al. investigated 37 clinical isolates of MRSA and found a high (>90%) degree of sensitivity for discriminating hVISA and VISA strains from vancomycin-susceptible strains [30]. This method may be suitable for centres with limited facilities to carry out PAP-AUC.

The question of whether vancomycin MIC creep is associated with clinical failure is critical. Some published studies report an association between therapeutic failure and vancomycin MICs [31–33]. In contrast, de Sanctis et al. found no association between elevated vancomycin MICs and treatment failure for MRSA infections [34]. Walraven et al. noted that the site of infection (e.g. endocarditis and pneumonia) rather than the vancomycin MIC was predictive of treatment failure, presumably reflecting the poor tissue distribution of vancomycin. It is of note that the vancomycin MIC_{90} (MIC at which ≥90% of strains are inhibited) of the MRSA strains isolated from patients included in this study was 2 μg/mL, making the interpretation difficult [35].

3. Development of new antistaphylococcal agents

In a meta-analysis of 22 studies, vancomycin MICs were significantly associated with mortality irrespective of the source of infection, although the effect was predominantly seen with bloodstream infections [odds ratio = 1.58, 95% confidence interval (CI) 1.06–2.37; $P = 0.03$] [36]. Furthermore, the breakpoint for mortality prediction for MRSA infections appears to be ≥1.5 μg/mL (using the E-test), which is lower than the reduced Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoint of ≤2 μg/mL (formerly ≤4 μg/mL). With bloodstream infections, the effect on mortality was more pronounced in infections with strains for which the vancomycin MICs were ≥1.5 μg/mL. Higher E-test MICs (which may remain in the CLSI susceptible range) may predict treatment failure because of poor antimicrobial efficacy, particularly when the drug in question is vancomycin, given its PK/PD properties (e.g. the AUC:MIC ratio of >400 is difficult to achieve at least in relation to strains with high MICs). However, it is possible that the elevated E-test MIC is simply a strain marker for changes in genetic loci, such as *agr* polymorphisms, that affect organism metabolism or virulence characteristics. Alternatively, hVISA strains may have been included in the meta-analysis data yielding vancomycin E-test MICs ≥2 μg/mL and this could potentially skew the data in favour of higher mortality. Whether the presence of hVISA strains was a significant confounding factor in the meta-analysis is open to question. Holmes et al. reported that while higher vancomycin MICs in MRSA strains were associated with treatment failure, the effect was also seen in MSSA strains for which the E-test vancomycin MICs were ≥1.5 μg/mL [7]. In other words, patients with MSSA infections treated with flucloxacillin had significantly worse outcomes if the infecting MSSA strain gave a vancomycin E-test MIC result that was ≥1.5 μg/mL [7]. Despite the drawbacks of the meta-analysis [36] and the fact that the use of vancomycin per se may not be associated with treatment failure [7], the findings of the meta-analysis highlight concern with the use of vancomycin for the treatment of MRSA infections in strains for which the vancomycin MICs were elevated (≥2 μg/mL by BMD or ≥1.5 μg/mL by E-test). Thus, there is a gap in the clinical management of serious MRSA infections even though it is not always possible to identify, with precision, patients who would have an unfavourable outcome with vancomycin. Data on newer agents have made it possible to identify areas where these agents could be used with some benefit. In the next section we discuss the data on some of the newly licensed agents active against MRSA.

4. Newer agents for the treatment of MRSA

The true efficacy of the newer agents against MRSA infections in comparison with vancomycin is unclear. The small number of cases of vancomycin-resistant *S. aureus* (VRSA) infection, for which vancomycin is of no benefit [37], is dwarfed by the number of VISA and hVISA cases reported. Several licensed and investigational agents appear to be effective for treating MRSA infections, although defining their precise use needs more study. In this section, we review some of the newer antimicrobials active against MRSA.

4.1. Oxazolidinones

4.1.1. Linezolid and tedizolid

Linezolid is the only currently licensed oxazolidinone in clinical practice. Its favourable PK/PD profiles are well known. Linezolid was compared with vancomycin in a randomised, double-blind, multicentre trial involving hospitalised adult patients with MRSA pneumonia (hospital-acquired or healthcare-associated). Patients received linezolid (600 mg twice daily) or vancomycin (15 mg/kg twice daily) for 7–14 days with adjustment of the vancomycin dose based on trough levels. Clinical success at the end of study was achieved in 95 (57.6%) of 165 patients on linezolid and 81 (46.6%) of 174 patients in the vancomycin group (per-protocol population), a difference that was statistically significant (95% CI for difference, 0.5% to 21.6%; $P = 0.042$). Patients on vancomycin were more likely to show signs of nephrotoxicity than those on linezolid (18.2% vs. 8.4%). The difference in clinical response was seen in various subgroup analyses. Thus, patients on mechanical ventilation receiving linezolid achieved a higher rate of clinical success (55.5% vs. 44.2%) as did patients with bacteraemia (44.4% vs. 31.6%). In terms of vancomycin MIC, the difference in response was less clear because of several factors. First, the number of patients with infections caused by strains for which the vancomycin MIC was >1 μg/mL was very small; second, the MICs were obtained by the BMD method rather than by the E-test method. None the less, the fact that the difference in clinical response was significant even when a vast majority of patients had MRSA infection with strains showing lower vancomycin MICs (≤1 μg/mL) remains noteworthy. Also, there was a correlation between microbiological response and clinical response, with patients on linezolid showing

a 30% greater clearance of MRSA. However, there was no statistical difference in mortality (Day 60), in contrast to the results of the previous trials by the investigators. This was due to improved survival among patients treated with vancomycin, which may have been due to greater attention paid to vancomycin dosing during the study period or because of the use of salvage therapy with linezolid in patients in the vancomycin arm. Thus, despite the lack of a demonstrable benefit in terms of survival (and noting that the study [38] was not aimed at demonstrating survival), the choice of therapy for MRSA hospital-acquired pneumonia must be considered cautiously, particularly due to concern of clinical failure when treating infections with strains with elevated vancomycin MICs but still within the susceptible range. Most international guidelines fall short of recommending linezolid as a first-line agent for the treatment of MRSA hospital-acquired pneumonia. These new data may impact on the existing recommendations.

The first description of linezolid resistance in *S. aureus* involved ribosomal mutations in the 50S subunit. An outbreak of linezolid resistance in 12 patients in a Spanish ICU was described in 2010 [39]. Strains of linezolid-resistant *S. aureus* isolated from patients during this outbreak harboured the plasmid-mediated *cfr* (chloramphenicol florfenicol resistance) gene rather than the G2675 T ribosomal mutation observed in enterococci [40]. The *cfr* gene encodes a methyltransferase that catalyses the methylation of A2503 in the 23S rRNA gene of the large ribosomal subunit, thereby conferring resistance to five different groups of antimicrobial agents including pleuromutilins, chloramphenicol, florfenicol, oxazolidinones and clindamycin. Several congeners of linezolid [e.g. tedizolid (formerly torezolid)] demonstrate activity against linezolid-resistant strains of staphylococci. Approximately 80% of MRSA strains are inhibited by tedizolid at $\leq$4 μg/mL. An in vivo MRSA mouse pneumonia model compared the efficacy of tedizolid to linezolid and vancomycin regimens. BALB/c mice were inoculated with MRSA and challenged with tedizolid (20 mg/kg once daily), linezolid (120 mg/kg twice daily) or vancomycin (25 mg/kg twice daily). On comparing the treatment groups with the controls, the investigators demonstrated a rise in bacterial load (1.1 log) in the controls and a reduction in bacterial load in all the three treatment groups at 24 h, i.e. a 1.2, 1.6 and 0.1 log reduction for tedizolid, linezolid and vancomycin, respectively, with no statistically significant difference between the two oxazolidinones. Vancomycin was less effective than both oxazolidinones (survival of 61.1% vs. 94.7% in the tedizolid group and 89.5% in the linezolid group) [41]. Similarly, a mouse thigh infection model demonstrated comparable efficacy for both tedizolid and linezolid [42]. In studies on human volunteers, administration of tedizolid (200 mg once daily for 3 days) led to concentrations in the epithelial lining fluid and alveolar macrophages that were, respectively, 40 and 20 times higher than mean plasma free drug levels [43].

A randomised, double-blind, phase 2 trial evaluated 200, 300 and 400 mg of oral tedizolid (once daily for 5–7 days) in patients with complicated skin and skin-structure infections (cSSSIs). MRSA isolates represented a large (76%) proportion of the bacteria recovered from the patients. Tedizolid MICs were lower compared with linezolid [MIC_{50} (MIC at which $\geq$50% of strains are inhibited) and MIC_{90} values of tedizolid against *S. aureus* (MSSA and MRSA) were both 0.25 μg/mL, whilst the MIC_{50} and MIC_{90} of linezolid were of 1 μg/mL and 2 μg/mL, respectively]. The overall microbiological eradication rates and the rates of clinical cure were high (both >95% for MSSA and MRSA in all three dosage groups) [44]. The greater potency of tedizolid (based on the MIC) could turn out to be significant, particularly if linezolid resistance becomes widespread. Tedizolid was active against linezolid-resistant strains for which the linezolid MICs ranged from 32 μg/mL to >128 μg/mL. However, the majority of strains in this study were coagulase-negative staphylococci (CoNS) [45].

4.2. Cephalosporins

4.2.1. Ceftaroline

Data from the CeftAroliNe Versus VAncomycin in Skin and Skin-Structure Infections (CANVAS) and the FOCUS trials are now available [46–49]. The merits and drawbacks of the CANVAS trials were briefly described in a previous consensus paper [3]. The FOCUS trials demonstrated that ceftaroline is an effective agent in the treatment of community-acquired pneumonia, but MRSA is less of a concern in this disease population subset. Since the publication of the previous consensus reports, several in vitro studies and case series have been completed focusing on the efficacy of ceftaroline against MRSA strains. Ho et al. [50] investigated the outcome of ceftaroline for indications not covered by its current licensed indications, i.e. therapy of bacterial community-acquired pneumonia and acute bacterial skin and skin-structure infections [51]. Six cases of recurrent MRSA bacteraemia (while on vancomycin or daptomycin therapy) and cases of endocarditis were reviewed by the authors [50]. Ceftaroline led to a rapid clearance of MRSA from the bloodstream and sterilisation of heart valves within 2 weeks of ceftaroline therapy. These data are encouraging given the high failure rate for *S. aureus* bacteraemia. Ceftaroline may fill two crucial unmet needs—bacteraemia and endocarditis—given its favourable PK/PD profile particularly at a higher frequency of administration (600 mg three times a day instead of twice daily). Ceftaroline is now licensed in the USA and Europe. The Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) Surveillance programme used the US Food and Drug Administration (FDA) susceptible breakpoint of $\leq$1 μg/mL and 98% of *S. aureus* strains had a ceftaroline MIC at or below this cut-off and none had MICs >2 μg/mL [52].

4.3. Newer glycopeptides

4.3.1. Telavancin

Telavancin is a lipoglycopeptide with multiple mechanisms of action. In a cSSSI study, telavancin was non-inferior to vancomycin, achieving 90% microbiological eradication in patients infected with MRSA [53]. Rubinstein et al. published the combined data from the Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia (ATTAIN) double-blind, phase 3 trials. A total of 1503 patients were randomised to receive the study medications. Cure rates with telavancin in the all-treated population were 58.9% compared with 59.5% for vancomycin (95% CI for the difference, −5.6% to 4.3%) for the all-treated population. In the clinically evaluable population (n = 654), cure rates with telavancin were 82.4% compared with 80.7% with vancomycin (95% CI for the difference, −4.3% to 7.7%). In the subset analysis, telavancin use was associated with higher cure rates in patients with monomicrobial *S. aureus* infection compared with vancomycin, but the cure rates in patients with MRSA infection were similar for both groups [54]. Since its licensing and availability, there have been further reports on the clinical use of telavancin in specific patient groups. Stryjewski et al. published a post hoc analysis of the Assessment of TeLAvancin in complicated Skin and skin-structure infections (ATLAS) trial, with a total of 1794 patients included in their data set. Patients with major abscesses, infective cellulitis and wound infections, and those with Panton–Valentine leukocidin-producing MRSA infections treated with telavancin had similar cure rates compared with patients who received vancomycin [55]. There are isolated case reports claiming successful clinical use of telavancin in MRSA mitral valve endocarditis following daptomycin failure [56], in polymicrobial osteomyelitis in combination with rifampicin and meropenem [57] and in prosthetic joint infection caused by meticillin-resistant CoNS [58].

4.3.2. Oritavancin

Oritavancin is a synthetic derivative of chloroeremomycin, a natural glycopeptide. Like vancomycin, it inhibits transglycosylation by binding to the terminal D-alanyl–D-alanine. Oritavancin also binds to the pentaglycyl bridge in the peptidoglycan moiety, which explains its activity against vancomycin-resistant bacteria such as vancomycin-resistant enterococci (VRE) and VRSA. Finally, oritavancin, like telavancin but unlike vancomycin, also causes cell membrane disruption, resulting in depolarisation and cell death [59].

The in vitro activity of oritavancin was assessed against 866 Gram-positive isolates, confirming its potent activity against a wide range of resistant MRSA, meticillin-resistant CoNS and VRE, including those resistant to newer agents such as daptomycin and linezolid [60].

With a half-life of 195 h, oritavancin is suitable for once-daily administration. In a phase 2 multicentre trial, 302 adult patients with cSSSI were randomised to three groups that received a daily dose of 200 mg for 3–7 days, a single dose of 1200 mg or a dose of 800 mg with an optional additional dose of 400 mg on Day 5. Clinical response was assessed between Days 21 and 29. The cure rates in the evaluable patients were 72.4% (55/76) in the daily-dose group, 81.5% (66/81) in the 1200 mg single-dose group and 77.5% (55/71) in the group with infrequent optional dosing. In patients with MRSA at baseline, the cure rates were 78.3% (18/23), 73.0% (27/37) and 87.0% (20/23), respectively, although the study did not have sufficient power to discriminate amongst the MRSA subgroup. There was no difference in the frequency of adverse effects in the three groups. Both single and infrequent dosing schedules of oritavancin were as effective as once-daily administration [61]. The FDA, however, did not approve oritavancin for the treatment of cSSSI as data in relation to MRSA were lacking. Since then, two studies (SOLO I and SOLO II) have been registered with ClinicalTrials.gov and both are expected to be undertaken soon.

4.4. Lipopeptides

4.4.1. Daptomycin

Daptomycin is rapidly bactericidal against *S. aureus* and exhibits concentration-dependent killing in vitro. Its activity is dependent upon the availability of calcium ions. Calcium ions enhance the activity of daptomycin in two ways: first, by inducing a conformational change leading to a charge-dependent oligomerisation and micelle formation; and second, by facilitating the binding of daptomycin with the acidic polysaccharide of the bacterial cell. Following this initial binding, the daptomycin molecule undergoes a structural alteration that allows it to penetrate deep into the membrane layer. It has been suggested that the micelles dissociate and deliver individual daptomycin molecules to the cell surface, which subsequently oligomerise internally [62]. Resistance to daptomycin is associated with mutations in the phospholipid biosynthesis gene including cardiolipin synthase (*cls2*) and the CDP-diacylglycerol-glycerol-3-phosphate 3-phosphatidyltransferase (*pgsA*) gene. The *mprF* mutation previously described leads to the synthesis of lysinated phosphatidylglycerol, thereby producing an overall positive surface charge that then causes electrorepulsion of daptomycin [63]. In this context, available data on β-lactam antibiotics and daptomycin combination treatment are relevant. β-Lactam agents by reducing the positive cell surface charge are able to counteract the repulsion of daptomycin, thus facilitating the binding of the latter to the cell surface [64]. In vitro data lend support to daptomycin/β-lactam combinations: addition of oxacillin to a medium containing daptomycin delayed the emergence of daptomycin-resistant mutants in one such model [65]. Dhand et al. report treating seven cases of MRSA that were refractory to therapy with vancomycin or daptomycin with a combination of antistaphylococcal β-lactam agents and daptomycin. All seven cases had rapid clearance of bacteraemia, and the in vitro experiment showed enhanced binding to daptomycin following exposure to nafcillin in one such strain. In addition, the investigators also confirmed a net reduction in the surface charge in the presence of oxacillin, and killing curves demonstrated enhanced killing by the antimicrobial combination [66]. Clinically, strains exhibiting daptomycin resistance are rarely encountered among MRSA; however, emergence of daptomycin resistance among hVISA strains has been reported in multiple studies. The genetic basis of resistance remains controversial. On the other hand, in other studies the clinical outcome of patients treated with daptomycin did not appear to be related to the vancomycin MIC [67]. Isolates from patients who are likely to receive daptomycin therapy should be tested for susceptibility to daptomycin by an MIC method such as BMD or E-test. Novel strategies have been used to treat patients with daptomycin-non-susceptible MRSA infections. In a patient with infective endocarditis, combination therapy with daptomycin and ceftaroline was successfully used to clear persistent bacteraemia [68]. High-dose daptomycin in combination with trimethoprim/sulfamethoxazole (TMP-SMX) has also been used to treat complicated infections with daptomycin-non-susceptible VISA strains [69]. In patients treated for osteomyelitis, Moenster et al. reported significantly reduced recurrence rates with daptomycin compared with vancomycin (29% vs. 61.7%) [70]. Finally, salvage therapy with high dose (≥8 mg/kg) daptomycin has been evaluated for the treatment of complicated bacteraemia, endocarditis, skin or wound infection, and bone and joint infection. Approximately 5% of patients developed breakthrough infection with daptomycin-non-susceptible strains [71].

5. Older agents

The development and commercialisation of new antimicrobial agents is complex and expensive. In this context, several older agents have the potential to be clinically useful. A phase 2 randomised study comparing loading (1500 mg twice daily on Day 1 followed by 600 mg twice daily) or non-loading (600 mg twice daily) dose regimens of fusidic acid with linezolid (600 mg twice daily) was recently reported. A total of 198 patients were enrolled. The high-dose fusidic acid regimen demonstrated comparable safety, tolerability and efficacy with linezolid for the treatment of acute skin and skin-structure infections. In the test-of-cure group, the success rates in the fusidic acid loading-dose group and the linezolid group in the intention-to-treat population were 85.9% and 94.8%, respectively [72]. Schmitz et al. randomised patients with uncomplicated skin abscesses into two groups; each group underwent incision and drainage followed by either TMP-SMX or placebo. TMP-SMX did not reduce treatment failure when compared with placebo but was associated with lower recurrence rates [73]. A retrospective investigation comparing TMP-SMX with vancomycin for the treatment of MRSA bacteraemia found similar 30-day mortality between the two groups (34.2% and 40.8% respectively) and a numerically lower rate of relapse in the TMP-SMX group [74]. Doxycycline and chloramphenicol have undergone trials, but in restricted settings. The resurrection of older compounds, e.g. pleuromutilins, is a welcome development [75]. Pleuromutilins were discovered in 1951 [76] and the first pleuromutilin for systemic use was tested in a phase 2 trial in 2011 [77]. It is difficult to predict whether some of these agents would be of benefit in the treatment of MRSA infections. Their use may delay the spread of resistance to the newer agents.

6. Conclusions

Despite significant developments in the management and treatment of MRSA infections, there are still important questions that remain unanswered regarding the optimal therapy for these infections. Even presumably objective assessments, such as the determination of MICs for vancomycin, often show a lack of correlation between various testing methods. In the absence of a precise laboratory method that predicts the efficacy of vancomycin (especially for hVISA strains), the early use of newer antimicrobial agents other than glycopeptides may be a more reliable option, particularly for invasive infections. Such a strategy obviously has drawbacks (e.g. cost) that must be balanced against the benefit of optimised early therapy. The challenge is to avoid inappropriate empirical therapy for invasive MRSA infections as this has been shown to be associated with higher mortality [4].

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None.

Competing interests

AMB has received speaker's honoraria from Pfizer and Astellas, has participated in advisory boards of Pfizer, and has received educational grants from Astellas, Pfizer and MSD. JG and IMG have received research grants and speaker's honoraria/consultancy fees from many manufacturers of MRSA-specific products. GRN is a member of the Australian advisory boards for Wyeth, AstraZeneca and Pfizer. AS is on the speaker's bureau of Pfizer and Novartis and has participated in advisory boards of Pfizer and Novartis. FCT is an employee and shareholder of Cepheid. All other authors declare no competing interests.

Ethical approval

Not required.

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