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Treatment of Methicillin-resistant *Staphylococcus Aureus*

Vancomycin and Beyond

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Abstract and Introduction

Abstract

There has been a welcome increase in the number of agents available for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). Vancomycin remains an acceptable treatment option, with moves toward individualized dosing to a pharmacokinetic/pharmacodynamic (PK/PD) target. Numerous practicalities, however, would need to be resolved before implementation. Lipoglycopeptides as a class show excellent in vitro potency. Their long half-lives and complex PKs may preclude these agents being used in critically ill patients. Anti-MRSA cephalosporins provide great promise in the treatment of MRSA. These agents, despite broad-spectrum activity, should be reserved for patients with MRSA infections as it is likely that usage will be associated with increased rates of resistance. Daptomycin is currently the only antibiotic to have shown noninferiority to vancomycin in the treatment of MRSA bacteremia. The results of an open-labeled trial to address the superiority of daptomycin compared with vancomycin in reduced vancomycin susceptibility infections are eagerly anticipated. No drug to date has shown superiority to vancomycin in the treatment of MRSA infections with the possible exception of linezolid in hospital-acquired pneumonia (HAP), making linezolid an important option in the treatment of MRSA-proven HAP. Whether these strengths and features are agent or class specific are unclear but will likely be answered with the marketing of tedizolid. There are insufficient data to recommend either quinupristin/dalfopristin or tigecycline, as first line in the treatment of severe MRSA infections. These agents however remain options in patients with no other alternatives.

Introduction

Staphylococcus aureus is a gram-positive bacterium that remains a troublesome pathogen especially within the hospital setting. This bacterium forms a part of the normal human nasal microflora and may cause infections in susceptible individuals especially in health care settings. What makes this bacterium a problem is its propensity to spread, especially in health care settings, and its remarkable capacity to evolve new antibiotic resistance. Not surprisingly therefore, *S. aureus* has been identified as one of the key "problem" bacteria in addition to *Enterococcus faecium*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species; these are the ESKAPE pathogens that urgently require development of new therapies.[1]

The overall burden of antimicrobial-resistant bacteria continues to increase and accounted for approximately 20% of all hospital infections in 2010.[2] These infections in turn are associated with increased patient morbidity and mortality.[3]

The rates of methicillin-resistant *S. aureus* (MRSA) are dynamic with current United States and European surveillance data suggesting that MRSA incidence has declined by between 27.7 and 54.2% in recent years.[4] Although these MRSA figures are encouraging, the impact of emerging community MRSA clones on health care-related infections is yet to become clear; regardless, MRSA infections are likely to continue to be a significant problem.

The purpose of this review is to explore the possible treatment options available for MRSA including new data related to vancomycin optimization. We will focus on initial therapy and not discuss issues surrounding either maintenance options, which generally following an extended period of parenteral therapy and usually consist of an oral agent, combination treatment or salvage therapy.

Vancomycin Optimization

Vancomycin was introduced in 1958 initially for the treatment of penicillin-resistant *S. aureus* but was quickly superseded by methicillin. Vancomycin rose to prominence following the emergence of MRSA and has been the mainstay of treatment for MRSA ever since. It is a glycopeptide with activity against gram-positive pathogens through inhibition of cell wall synthesis.[5,6] Although, vancomycin has been used for over 50 years, multiple controversies still exist about the optimum usage of this agent.

Pharmacokinetic/Pharmacodynamic Considerations

The pharmacokinetic/pharmacodynamic (PK/PD) parameter that best predicts vancomycin efficacy is the ratio of the area under the 24-hour concentration curve (AUC) to the minimum inhibitory concentration (MIC) of the infecting organism (AUC/MIC).[7–9] Moise et al investigated the utility of AUC/MIC in predicting the clinical and microbiological success of vancomycin treatment in a single-center study of 62 patients with *S. aureus* pneumonia (the majority of whom had ventilator-associated pneumonia [VAP]).[10] Using classification and regression tree analysis, vancomycin AUC/MICs of greater than 345 and 866 were associated with clinical and microbiological success, respectively. On the basis of these data, and a subsequent validation study by the same authors in *S. aureus* pneumonia,[11] a vancomycin AUC/MIC of ≥ 400 has been recommended in consensus guidelines to predict successful therapy.[9]

Individualizing the vancomycin exposure–response relationship by dosing vancomycin to attain this PK/PD target may improve clinical outcomes. However, clinicians should be aware of the inherent variability that exists between methods used to obtain either AUC or MIC values and the expertise required to implement such a practice.

AUC Measurements and Therapeutic Drug Monitoring

There are several methods that can be employed to obtain the AUC;[12] and include determination based on multiple sampling in a dosing interval; calculations based on PK data (trough levels); Bayesian modelling and AUC calculations using a simple formula based on daily vancomycin dose and creatinine clearance (Eq. [1]). In most cases the Cockcroft–Gault equation is used as a measure of creatinine clearance. The most accurate (i.e., the closest to the true AUC value), remains actual AUC measurements followed by Bayesian methods using population data and formula-based methods.[13]

Currently, the most feasible and practical method for AUC determination remains using a surrogate measure, serum trough concentrations, despite poor accuracy when compared with the above methods.[13] Trough levels between 15 and 20 µg/mL are recommended based on the original modelling data and correspond with attaining a AUC/MIC target > 400 provided that the MIC of the organism is ≤ 1 µg/mL.[9,14,15] Conversely, the probability of target attainment is less likely in high vancomycin MIC infections and this has been the main rationale for alternative antimicrobial therapy in these situations.[16,17]

Consensus guidelines recommend serum trough concentrations be taken at steady state,[9] and it is important to realize that the timing of sample collection (a trough level, i.e., before the next dose) is vital to maintain accuracy of vancomycin dose adjustments.[18]

Dosing Considerations

Vancomycin is usually administered through intermittent dosing. Due to the importance of achieving therapeutic vancomycin serum concentrations early in the course of infection, a loading dose of vancomycin have been proposed especially in seriously ill patients.[9,19–21] Continuous infusions have also been proposed as faster achievement of target concentrations and less variability in serum concentrations and AUC have been observed with continuous infusions.[22,23] Although no improved clinical outcomes have yet been reported with such a strategy, continuous infusion have been associated with lower rates of nephrotoxicity and a higher steady state concentration, with the nephrotoxicity threshold around 28 µg/mL compared with intermittent infusions.[24,25]

Minimum Inhibitory Concentration Determinations

The denominator of the PK/PD equation, the MIC result, varies between methodologies,[26,27] which in turn have a significant impact on the final ratio.[28] Few diagnostic laboratories routinely perform the reference broth microdilution (BMD) method for MIC determination and instead use a gradient diffusion method such as Etest (bioMérieux, Inc., Durham, NC) that is less expensive and less labor-intensive. Similarly, automated antibiotic susceptibility platform results differ from BMD and Etest and as such clinicians need to take into account MIC methodology in AUC/MIC target determination.[29]

The Optimal AUC Target

Several clinical studies have evaluated the vancomycin AUC/MIC target associated with outcome. The vancomycin AUC/MIC target varies among these studies, secondary to the variability in AUC calculation, MIC methodology, clinical *S. aureus* infection syndrome, and outcomes measured (). Reassuringly, observed targets tend to be similar between studies and comparable to the original and recommended AUC/MIC target (i.e., > 400) when employing similar methodology. It is important to note, however, that these studies have all examined vancomycin AUC within the first 96 hours and currently there are no randomized controlled studies that examine whether adjustment of vancomycin dosing regimens prospectively during a treatment course to achieve specific target AUC/MIC ratios are associated with improved clinical outcomes.

Table 1. Comparison of vancomycin AUC/MIC calculations and impact on clinical outcomes in *Staphylococcus aureus* infection

Publication year/reference	No.	Clinical syndrome	Outcome	MIC methodology and observed AUC/MIC target
Formula-based[a] AUC determination using Cockcroft–Gault equation to estimate renal function				
2000[10]	62	MSSA and MRSA pneumonia	Treatment success	BMD > 345 clinical BMD > 866 microbiological
2004[11]	90	MSSA and MRSA pneumonia	Treatment success	BMD > 350 clinical BMD ≥ 400 microbiological
2010[30]	222	MSSA and MRSA bacteremia	Persistent bacteremia	No target detected
2013[28]	182	MSSA and MRSA bacteremia	Mortality	BMD < 373
2014[31]	127	MRSA bacteremia	Treatment failure	BMD < 398 Etest < 270
Formula-based[a] AUC determination using population-based vancomycin clearances				
2011[32]	320	MRSA bacteremia	Treatment failure	Etest < 421
2013[33]	35	MRSA bacteremia with septic shock	In-hospital mortality	BMD < 451
Formula-based[a] AUC determination using pharmacokinetic data and Bayesian modelling				
2012[34]	50	Complicated MRSA bacteremia and endocarditis	Attributable mortality	Etest < 211

2013[35]	59	MRSA bacteremia osteomyelitis	Bacterial clearance	BMD > 293
2014[36]	76	MRSA infections	Treatment failure	BMD < 430 Etest < 399
2014[13]	123	MRSA bacteremia	Treatment failure	BMD < 521 Etest < 303

Abbreviations: AUC, area under the 24-hour concentration curve; BMD, broth microdilution; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus* aureus; MSSA, methicillin-sensitive *Staphylococcus aureus*.

Note: Etest (bioMérieux, Inc., Durham, NC).

[a] See Eq. (1) for the formula.

Eq. (1) shows the formula for area under the 24-hour concentration curve (AUC):

$$AUC_{24} = \frac{D}{([CLCr \times 0.79) + 15.4] \times 0.06}$$

where D, total vancomycin dose in 24 hours; CLCr, creatinine clearance calculated by various methods.

Ongoing and Unresolved Controversies

The current vancomycin MIC susceptibility breakpoint is 2 µg/mL.[37] Debate exists whether the current breakpoint needs to be lowered, as infections caused by isolates with an elevated or high vancomycin MIC (at the upper end of the susceptible range; ≤ 2 µg/mL) are associated with worse clinical outcomes.[38] In addition, as discussed above, PK/PD target attainment is unlikely with current vancomycin dosing for these infections.[17] Controversy exists however, as outcomes with these infections may not reflect antibiotic failure per se but may rather be a marker for some other pathogen or host characteristic. This is best illustrated by two studies that observed a similar association with high vancomycin MIC and outcomes in methicillin-sensitive *S. aureus* (MSSA) infections treated with flucloxacillin.[39,40] Similarly, certain strains known as heterogeneous vancomycin-intermediate *S. aureus* (hVISA); which contain a subpopulation of VISA, are associated with comparable clinical outcomes to vancomycin susceptible *S. aureus* infections,[41–43] despite having elevated MICs (predominantly around 2 µg/mL) in routine laboratory testing. Possible explanations include the reduced virulence[44] and lower rates of shock[45] observed with hVISA. Considering all the above data, and that no new antimicrobial agents had demonstrated superiority over vancomycin in clinical trials, the Infectious Diseases Society of America MRSA treatment guidelines at the time of publication recommended vancomycin as first-line therapy regardless of the vancomycin MIC and switching to alternative therapy if there is documented clinical or microbiologic failure.[16] For isolates with an MIC > 2 µg/mL there is no role for vancomycin and an alternative agent should be administered.

Despite these complexities and controversies, vancomycin is likely to remain an option for the treatment of MRSA. However, dose optimization by way of individualized dosing toward a PK/PD target will probably be recommended in the future, albeit in selected patient groups where antibiotic therapy significantly impacts outcomes (e.g., critically ill).

Teicoplanin. Teicoplanin is a glycopeptide with a similar mode of action to vancomycin. Much debate has

surrounded this antibiotic, however, due to data showing inferior efficacy compared with vancomycin.[46] These results can be explained by inadequate dosing of teicoplanin secondary to greater protein binding compared with vancomycin.[47] Recent data and a meta-analysis both conclude that teicoplanin (at higher and appropriate dosing) is not inferior to vancomycin,[48,49] and may be associated with a lower rate of adverse events.[48] Higher teicoplanin MICs have also been associated with poor clinical outcomes and increased mortality in teicoplanin-treated patients with MRSA bacteremia and pneumonia,[50,51] mirroring the phenomenon observed with high vancomycin MIC infection. Teicoplanin is not currently available in the United States.

Lipoglycopeptides. Oritavancin, telavancin, and dalbavancin are semisynthetic lipopolypeptide analogues of vancomycin with activity against MRSA. In common with vancomycin, they each contain a heptapeptide core that enables inhibition of cell wall synthesis. Each agent also contains a lipophilic side chain that prolongs their half-life and increases their activity against gram-positive cocci by greater binding to peptidoglycan precursors to prevent cell wall synthesis. Oritavancin and telavancin also disrupt membrane barrier function of *S. aureus*.[52,53,54] All three drugs have activity against MRSA and VISA, oritavancin,[55] dalbavancin,[56] and telavancin[57] have activity against vancomycin-resistant *S. aureus* (VRSA).

Telavancin. The lipophilic side chain of telavancin confers enhanced potency, with approximately 10-fold more potency than vancomycin. It has in vitro activity against MRSA, VISA, daptomycin nonsusceptible and linezolid nonsusceptible *S. aureus*.[53,58,59] In vitro studies of hVISA clinical strains suggest that telavancin has superior bactericidal activity compared with vancomycin and linezolid.[60]

Telavancin was approved in November 2009 in the United States for the treatment of acute bacterial skin and skin structure infections (ABSSSI), however the marketing application for this indication in Europe was withdrawn in October 2008 due to concerns in the review process such as lack of additional benefit over vancomycin, potential increased nephrotoxicity compared with vancomycin, possible increased QT prolongation, and possible impurities in the production process.[61] It was granted marketing approval in May 2011 in Europe and in June 2013 in the United States (with a black box warning) for hospital-acquired pneumonia (HAP) caused by gram-positive pathogens including MRSA where alternative treatments are not suitable based on the results of the ATTAIN studies.[62] Of note, comparable cure rates were noted in patients with MRSA HAP (81.8% for telavancin vs. 74.1% for vancomycin). A posthoc analysis of these studies demonstrated comparable 28-day overall survival rates between the two groups; however lower survival was observed in telavancin-treated patients with moderate-to-severe renal insufficiency (creatinine clearance < 50 mL/min and < 30 mL/min, respectively), consequently the black box warning in the United States.[63]

A randomized phase two clinical trial (the ASSURE study) was recently published evaluating intravenous telavancin 10 mg/kg once daily compared with comparators (intravenous vancomycin 1 g twice daily or intravenous antistaphylococcal penicillin 2 g 6 hourly) for the treatment of uncomplicated *S. aureus* bacteremia (SAB).[64] Similar cure rates were seen between both groups at a test-of-cure visit scheduled at 84 days after commencement of study medication. Although drug discontinuation rates were similar in both treatment arms, adverse events were more frequent with telavancin, notably clinically significant elevations in serum creatinine.[64] Although MRSA bacteremia accounted for almost half of the patients enrolled in this study (15/31) only nine patients were in the clinically evaluable population precluding any treatment recommendations at this stage.

QT prolongation is a recognized adverse event of telavancin, with the risk reported to be similar to fluoroquinolones.[64–66] To date, no cardiovascular events attributed to QT prolongation have been reported. Transient elevations in serum creatinine and thrombocytopenia have also been observed.[62,66]

Dalbavancin. Dalbavancin is a lipoglycopeptide derived from teicoplanin. It has a prolonged terminal half-life up to 250 hours, which allows once weekly dosing.[58,67,68] Compared with vancomycin and daptomycin, it has 8- to 16-fold more activity against MRSA, hVISA, and VISA with typical MICs ranges between ≤ 0.03 and 0.12 µg/mL for MSSA and MRSA.[69,70] Clinical trials have been performed in ABSSSI but not invasive infections. DISCOVER 1 and 2 were studies comparing intravenous dalbavancin 1 g on day 1 followed by 500 mg on day 8

with intravenous vancomycin 1 g or 15 mg/kg twice daily (for a minimum of 3 days) plus a step–down to oral linezolid 600 mg twice-daily to complete 10 to 14 days of treatment.[71] To obtain possible registration by the U.S. Food and Drug Administration (FDA), these studies were required to utilize stricter enrolment criteria, which included larger areas of erythema or greater complexity with abscess formation, and were required to measure clinical response at 48 to 72 hours.[72] Consequently, unlike previous skin and soft tissue trials, patients enrolled in the DISCOVER studies were more likely to be systemically unwell (more than 85% with fever, 50% had the systemic inflammatory response syndrome) with a greater burden of infection (the area of erythema was ~4-fold the FDA requirement). Overall, dalbavancin was noninferior to the comparator arm, including the subset of patients with MRSA with few observed adverse effects mainly comprising gastrointestinal upset and pruritus.[71] Based on these data, dalbavancin received FDA approval for ABSSSI in the United States in May 2014, and it is currently under review in Europe.

Oritavancin. Oritavancin is a lipoglycopeptide derived from vancomycin and is rapidly bactericidal with extensive tissue distribution.[73,74] Not surprisingly, preclinical studies suggest highly variable dosing strategies between 200 and 1,200 mg.[58] Like dalbavancin it has a prolonged half-life up to 393 hours. The comparable potency of oritavancin is less clear as previous MICs results are inaccurate, as the drug has been found to stick to plastic tubes and microdilution wells, affecting the final MIC result. This phenomenon can be overcome by the addition of 0.002% polysorbate 80.[75] Regardless of these in vitro issues, oritavancin retains activity against hVISA, VISA, and VRSA strains.[76,77] In addition, it has activity against *mecC* MRSA,[78] and remains highly effective against multidrug resistant *S. aureus* clinical isolates.[76,79]

Like dalbavancin, there are no clinical studies in invasive infection and there are no clinical trials registered with ClinicalTrials.gov for the treatment of bacteremia or endocarditis. SOLO 1 and 2 were multicenter randomized double-blind studies evaluating a single dose of intravenous oritavancin 1,200 mg compared with intravenous vancomycin 1 g or 15 mg/kg twice daily for the treatment of ABSSSI thought or proven to be caused by a gram-positive pathogen. Results from SOLO 1 were recently published showing noninferiority of oritavancin compared with vancomycin for the primary composite endpoint of early clinical evaluation at 48 to 72 hours, including the subset of patients with MRSA-proven ABSSSI.[80] Despite concerns about QT prolongation similar to telavancin, there were no significant differences in electrocardiogram findings with adverse effects and rates of discontinuation similar between the two treatment groups. This study also recruited patients using the new stricter FDA criteria, and patients in SOLO 1 were sicker than those in DISCOVER 1 and 2.[81] Oritavancin was recently granted regulatory approval in August 2014 in the United States, and it is currently under priority review in Europe.

Anti-MRSA Cephalosporins. In the treatment of MSSA infections, β-lactams are associated with improved clinical outcomes when compared with vancomycin or glycopeptides.[82–86] These data are so compelling that guidelines state that vancomycin should be avoided in the treatment of MSSA infections unless the patients has a significant β-lactam allergy. Thus the discovery of two cephalosporins (β-lactams), ceftaroline and ceftobiprole with in vitro activity against MRSA due to their affinity for the penicillin-binding protein PBP2a,[87,88,89,90] offer great promise in the treatment of MRSA.

Ceftaroline. Ceftaroline is highly active against MSSA and MRSA,[91,92] hVISA and VISA,[93,94] and against daptomycin nonsusceptible *S. aureus*.[95]

Ceftaroline has already been approved for use in the treatment of ABSSSI and community-acquired pneumonia (CAP). It is important to note that the initial licensing studies for pneumonia specifically excluded patients with risk factors for MRSA pneumonia due to the inactivity of the comparator drug ceftriaxone.[96] There are no randomized controlled trial (RCT) data for more invasive infections, such as bacteremia, endocarditis or osteoarticular infections, however results from case reports and series are encouraging.[97–102] Likewise, ceftaroline in combination as salvage therapy has been effective in patients with persistent MRSA bacteremia.[103]

Results are yet to be published from a RCT in patients with community-acquired bacterial pneumonia at risk of

MRSA infection that was completed in December 2013 (ClinicalTrials.gov NCT01645735), and compared intravenous ceftaroline 600 mg 8 hourly versus intravenous ceftriaxone 2 g once daily plus intravenous vancomycin 15 mg/kg twice daily (and adjusted based on trough concentrations). A multicenter open-label cohort study evaluating the safety and efficacy of intravenous ceftaroline 600 mg 8 hourly in SAB including MRSA bacteremia was recently completed in July 2014 (ClinicalTrials.gov NCT01701219).

Adverse events with ceftaroline are similar to those of other cephalosporins. Headache, rash, and infusion-related adverse events have been reported at rates similar to or less than comparator agents.[96,100] Transient elevations in liver transaminases and creatinine kinase and the formation of urinary crystals have been reported. The clinical significance of urinary crystals is uncertain but do not represent crystallized drug. Increased rates of hematologic toxicity and rash leading to discontinuation have been reported in off-label use.[104] In addition, eosinophilic pneumonia has been reported when using ceftaroline for MRSA pneumonia.[102,105,106]

Clinically significant resistance has not yet been reported in clinical settings. An in vitro study of stored MRSA isolates in Australia has demonstrated ceftaroline nonsusceptibility in ST239 MRSA, a multiresistant MRSA strain endemic in hospitals in the Asia-Pacific.[107] In addition, ceftaroline heteroresistance has been observed in MRSA, hVISA, VISA, daptomycin nonsusceptible, and linezolid nonsusceptible *S. aureus* laboratory isolates[108] with mutations seen in PBP2a leading to lower binding affinity, reduced efficacy, and higher ceftaroline MICs.[109,110]

Ceftobiprole

Ceftobiprole is another antistaphylococcal cephalosporin with greater spectrum of activity than ceftaroline. Similar to ceftaroline, it retains activity against more resistant *S. aureus* strains including those with elevated vancomycin MIC.[111] Studies in ABSSSI demonstrated noninferiority to vancomycin,[112] and it was approved for use in Canada, Switzerland, Ukraine, Russia, Azerbaijan, and Hong Kong.[113] Due to concerns about data integrity, both the United States and Europe denied approval for this indication in 2009 to 2010. In a RCT of patients requiring hospitalization for CAP, intravenous ceftobiprole 500 mg twice daily was noninferior to intravenous ceftriaxone 2 g once daily with or without intravenous linezolid 600 mg twice daily,[114] however in the microbiologically evaluable population there was only one patient with MRSA pneumonia. Intravenous ceftobiprole 500 mg 8 hourly was also noninferior to intravenous ceftazidime 2 g 8 hourly plus intravenous linezolid 600 mg twice daily in the treatment of HAP but not VAP.[115] Favorable rates of clinical cure and microbiological eradication were observed in those patients with MRSA pneumonia. In a posthoc PK/PD model there was a strong correlation between ceftobiprole exposure and improved clinical cure and microbiological eradication.[116]

Ceftobiprole gained regulatory approval in October 2013 in 12 European states (Austria, Belgium, Denmark, Finland, France, Germany, Norway, Spain, Sweden, and the United Kingdom) for the treatment of CAP and HAP, however it has not been approved for the treatment of VAP.[117,118] Basilea Pharmaceutica (Basel, Switzerland) does not intend on initiating new phase three trials for ceftobiprole to seek potential regulatory approval in the United States.[119] It has a comparable adverse effect profile to comparators, similar to other cephalosporins.[112,114,115]

Daptomycin. Daptomycin belongs to a new cyclic lipopeptide class of antibiotics and was first licensed for human use in 2003. It has a unique mechanism of action, with calcium-dependent binding to the cytoplasmic membrane resulting in rapid membrane depolarization and efflux of potassium.[120,121] This results in the arrest of DNA, RNA, and protein synthesis and leads to rapid cell death. Importantly, daptomycin is inactivated by pulmonary surfactant and cannot be used in the treatment of pneumonia. It also has poor penetration into cerebrospinal fluid, although this may improve in the setting of inflamed meninges.[122]

Daptomycin is active against methicillin- and vancomycin-resistant staphylococci, and is the only new antibiotic that has a licensing indication for the treatment of SAB and right-sided endocarditis.[123] Historically, daptomycin has been used as salvage therapy in patients failing vancomycin therapy, particularly with high vancomycin MIC infections, but increasingly it is being used as initial therapy in high inoculum MRSA infections. For example, a

recent case–control study by Moore et al demonstrated improved survival and lower rates of clinical failure when daptomycin was used in the treatment of high vancomycin MIC MRSA bacteremia, whether as salvage treatment or as early initial treatment.[124] Although this study suggested better outcomes in elevated vancomycin MIC infections, the results should be interpreted with caution secondary to methodological limitations including a selection bias. A subsequent study attempted to address this issue by selecting patients using a propensity score matching procedure.[125] Despite showing a mortality benefit with daptomycin compared with vancomycin at 30 days, several limitations preclude generalization of these results; these include the MIC methodology used (automated susceptibility platform) in the study and the small number of patients recruited (~10% of all screened patients).

A multicenter open-label RCT is currently recruiting patients to investigate whether intravenous daptomycin 6 to 8 mg/kg daily is superior to intravenous vancomycin 15 mg/kg twice daily (and adjusted by trough levels thereafter) in the treatment of MRSA bacteremia with high vancomycin MIC (ClinicalTrials.gov NCT01975662). Hopefully this study will be completed and be able to answer this important question as a similar previous study had to be terminated due to low patient enrollment (ClinicalTrials.gov NCT01287832).

Unfortunately daptomycin has not been the panacea once predicted for treatment of MRSA. Resistance emerged within months of its commercial use,[126] and in the original licensing study for SAB it was noted that one-third of daptomycin treatment failures were associated with reduced susceptibility to daptomycin.[123] Prior exposure to vancomycin and retained prosthetic devices have been associated with an increased risk of daptomycin resistance,[121,127] as well as doses less than 6 mg/kg (the FDA-licensed dose for SAB and endocarditis) for serious infections such as bacteremia and endocarditis.[128] This is reflected in the Infectious Diseases Society of America guidelines for treatment of MRSA infections, where daptomycin dosing is recommended at 8 to 10 mg/kg for complicated bacteremia and in combination with other agents if there has been prior vancomycin treatment failure.[16] Improved outcomes have been reported if high-dose daptomycin is instituted early in patients with high vancomycin MIC MRSA bacteremia,[125,128] although resistance has now been reported in high dose therapy.[129]

Daptomycin nonsusceptibility mechanisms are diverse, and are most frequently observed in patients with high bacterial burden infections or ineradicable foci.[129,130] Various single nucleotide polymorphisms have been observed with *mprF* mutations generally selected following daptomycin exposure.[131] Mutations in regulators of cell wall metabolism, such as *walKR* and cell wall thickening, which are selected for by failing vancomycin therapy, may result in daptomycin cross-resistance.[132,133] This explains the observed association between daptomycin resistance and reduced vancomycin susceptibility as occurs in hVISA and VISA isolates.[131] Not surprisingly, this cross-resistance has been documented in vitro and in vivo in the absence of prior daptomycin exposure and is largely a clinical problem in the setting of daptomycin salvage therapy.[134,135]

Linezolid. Linezolid is an oxazolidinone class antibiotic that inhibits bacterial protein synthesis by preventing the formation of the 70S initiation complex with activity against MRSA. Unlike, vancomycin, linezolid achieves high levels in the epithelial lining fluid of the lungs, making it a promising candidate for treatment of patients with HAP, including MRSA. This advantage was subsequently highlighted when a posthoc review of subgroups from two studies showed a survival advantage.[136] However, the results were received with caution given the study methodology.

To provide the definitive answer to this question Wunderink et al conducted a multicenter RCT comparing vancomycin to linezolid in the treatment of MRSA pneumonia.[137] This study included 448 patients with MRSA pneumonia in a modified intention-to-treat population and 348 in a per-protocol population. Both clinical and microbiological cure rates were significantly higher in the linezolid arm compared with vancomycin. The key strength of this study is that it was specifically designed to investigate the comparative efficacy of linezolid to vancomycin for MRSA pneumonia. However, despite stringent randomization, by chance the vancomycin arm had a higher proportion of patients on mechanical ventilation (74% in vancomycin arm vs. 67% in linezolid arm) and with MRSA bacteremia (11 vs. 5%). The study was designed using current vancomycin-dosing regimens, at the time which, based on the recent guidelines, would be considered suboptimal. However, the most discussed

finding was the similar 60-day mortality in both treatment arms (vancomycin 17%, linezolid 16%), despite the greater clinical and microbiological cure rates with linezolid. Possible explanations for this finding include that the study was not powered to detect a mortality difference; and that antibiotics are likely to influence attributable mortality rather than overall mortality especially in critically ill patients. Given this controversy, four subsequent meta-analyses have been conducted and have consistently shown similar efficacies for linezolid and vancomycin for treatment of HAP.[138–141] The two most recent of these meta-analyses included the data from the above trial[138,139] and observed similar efficacies for linezolid and vancomycin, including microbiologically proven MRSA pneumonia subgroups.

Linezolid has been compared with vancomycin for SAB in several case series and observational cohorts.[142–145] Comparable efficacy to vancomycin, in terms of clinical outcomes and mortality, was observed in all studies including meta-analyses for the subgroup of patients with SAB.[146,147]

Tedizolid. Tedizolid (previously known as torezolid during early studies) is a new oxazolidinone that has been specifically engineered to improve bioavailability and efficacy but reduce toxicity compared with linezolid. It is dosed once daily and its potency is 4 to 16 times greater than linezolid,[58,148] with activity against linezolid nonsusceptible *S. aureus* isolates.[61,148,149] Data on its activity against VISA and VRSA are lacking.[58,150,151] The ESTABLISH-1 trial was a phase three randomized controlled study demonstrating noninferiority of oral tedizolid 200 mg once daily for 6 days compared with oral linezolid 600 mg twice daily for 10 days for treatment of ABSSSI.[152] Both oral and intravenous formulations were licensed in the United States in June 2014, and it is currently under evaluation in Europe compared with linezolid, tedizolid has less myelotoxicity and gastrointestinal disturbance.[149,153] In addition, the risk of serotonergic syndrome is negligible due to a lack of monoamine oxidase inhibition at clinically relevant doses.[153]

Quinupristin/Dalfopristin. Quinupristin/dalfopristin (QD) is a combination of two semisynthetic streptogramin antibiotics (derived from pristinamycin) in a ratio of 30:70. QD binds to the 50S bacterial ribosome in two sequential steps, and thus inhibits bacterial protein synthesis. Each drug alone is bacteriostatic against susceptible gram-positive organisms including MRSA, but the combination is synergistic and bactericidal.[154]

In vitro data reveal that QD is broadly active against MRSA isolates, with an MIC_{50} of 0.5 μg/mL and an MIC_{90} of 1.0 μg/mL in a study of 10,216 clinical MRSA isolates from the United States and Canada.[155] Furthermore, the MICs of QD against MRSA were not significantly different from those against MSSA. A subsequent study including isolates from Europe and Asia as well as the Americas had similar findings, with over 99% of MRSA isolates susceptible.[156] QD has several notable adverse effects which limit its use, including pain on injection in up to 50% of patients (necessitating administration through a central venous catheter), myalgias, arthralgias, nausea, and hyperbilirubinemia, each occurring in approximately 10% of patients in clinical studies.[157,158]

There are no large clinical trials comparing QD with vancomycin or other treatments for severe MRSA infections. Animal models show mixed results, with QD showing rapid bactericidal activity in a *S. aureus* mouse endocarditis model,[159] but showing inferior results to vancomycin in both a rabbit arthritis model[160] and an MRSA rabbit endocarditis model.[161]

Most clinical studies of QD have included patients with various gram-positive infections, and the number with MRSA in these studies is quite small. In a multicenter international RCT comparing QD with vancomycin in 298 patients with gram-positive nosocomial pneumonia, QD had similar clinical success (43.3%) to vancomycin (45.3%) in the all-treated group, but a trend to lower clinical success in the subgroup with proven MRSA infection (19% in the QD group vs. 40% in the vancomycin-treated arm).[158] In phase 2 RCT comparing QD with standard therapy in patients hospitalized with ABSSSIs, seven of nine patients with proven MRSA infections treated with QD had a successful outcome.[162]

The largest published study of the clinical use of QD in severe infections was the report from an open label emergency use program for patients either intolerant of all other options or who had failed previous therapy and had no other available options.[157] This program enrolled 90 patients from 63 centers in 5 countries. Allergy to

or intolerance of other antibiotic options was the reason for enrolment in the majority of patients (70%). Of the 90 enrolled patients, 70 were for culture-proven MRSA with osteoarticular (*n* = 40), ABSSSI (*n* = 15), and endocarditis (*n* = 11) being the most common foci of infection. Overall 43 patients were bacteremia. The success at days 7 to 14 was 71%, which is not dissimilar to a pooled clinical success rate of 78% from a meta-analysis of 11 RCTs of vancomycin for MRSA infections.[163] However, this report contained concerning signals in the subgroup with severe infections, with an overall success rate of only 55% in endocarditis and 40% with pneumonia.[163]

Tigecycline. Tigecycline is a parenteral glycylcycline antibiotic, derived from minocycline. It has in vitro activity against many gram-positive bacteria, including MRSA. The main treatment-limiting adverse effect of tigecycline is nausea and vomiting, which occurs in 30 to 40% of treated patients.[164,165]

There are substantial clinical trial data available on the use of tigecycline for intra-abdominal infections, complicated ABSSSIs, and nosocomial pneumonia, but there are insufficient data available specifically assessing the role of tigecycline in invasive MRSA infections. Multiple studies have assessed the in vitro tigecycline susceptibility of various MRSA strains and they have consistently found that tigecycline is highly active against MRSA in vitro. For example, two studies from the United States found 98.2% of 1,989 community-acquired MRSA isolates[166] and 100% of 1,692 unselected MRSA isolates[167] were susceptible. European studies have had similar findings.[168,169]

In animal models, tigecycline has comparable activity to vancomycin against MRSA, in a MRSA rat thigh infection model[170] and to teicoplanin in a rabbit osteomyelitis model.[171] In most randomized trials, there are too few MRSA patients to draw conclusions from. For example, in a phase 3b RCT of 571 patients with complicated ABSSSIs, the overall cure rate was 77.5% in the tigecycline group overall, and 69% in the 36 patients with MRSA infection.[172] In a RCT of high-dose tigecycline in 108 patients with HAP, there were only 6 patients with proven MRSA infections.[173] The only RCT to focus on MRSA patients was a phase 3 RCT enrolling patients with MRSA or vancomycin-resistant enterococcal infections.[165] Of the 117 microbiologically evaluable MRSA patients, the clinical cure rate was comparable in the tigecycline group (81.4%) to vancomycin or linezolid (83.9%).

The FDA issued a safety warning in 2010 and a black box warning in 2013 regarding increased risk of mortality in patients treated with tigecycline compared with other antibiotics. These warnings prompted several meta-analyses to be published, most of which had similar findings: a small but significant excess mortality risk in the tigecycline arm over the comparator arm in RCTs of serious infections,[164,174–176] particularly patients with bacteremia and VAP.[177] The number of patients with proven MRSA infections in these meta-analyses was either small or not specified, but subgroup analysis by organism type (gram-positive vs. gram-negative) found no difference in the mortality excess by organism type.[164,175] The paradox of higher mortality and lower cure despite excellent in vitro activity is thought to be due to PK/PD considerations including high protein biding, an inadequate AUC/MIC with standard dosing, poor serum concentrations, and penetration into some tissues.[173,178,179,180]

Conclusions

In the treatment of MRSA, vancomycin remains a viable option. Despite this antibiotic being in clinical use for over 50 years there still remains uncertainty about the best dosing strategy. However, new insights suggest improved outcomes when dosing to a PK/PD target. The implications of these observations are a move toward individualized dosing. However, before implementation, numerous practicalities need to be resolved including real-time AUC measurements or calculation and appropriate expertise to interpret the results and make appropriate modifications. Until these hurdles are addressed it is likely that we will continue to dose using an AUC surrogate such as vancomycin trough concentrations. It should be noted that aggressive dosing and appropriate sampling (i.e., trough levels) are required to make suitable dose modifications. Nevertheless, individualized dosing should be explored in selected patient populations like the critically ill or in intensive care.

Lipoglycopeptides as a class, representing three agents, all show in vitro potency greater than vancomycin.

However, their long half-lives and complex PKs (especially oritavancin) may preclude these agents being used in critically ill patients. In addition, the black box warning associated with telavancin would further reduce its current role. Nevertheless, these agents provide some alternatives when no other options are available.

Anti-MRSA cephalosporins (ceftobiprole and ceftaroline) provide great promise in the treatment of MRSA. Their clinical utility remains to be seen, however, as resistance has already been observed in vitro with likely identified mutations; consequently, monitoring for broader emergence of resistance will be required. Ceftobiprole is a viable option in the treatment of CAP and HAP with results yet to be published for ceftaroline. Similarly, a bacteremia study comparing ceftaroline to vancomycin has only just been completed. Nevertheless, these agents should be reserved for patients with MRSA infections as it is likely that usage will be associated with increased rates resistance.

Daptomycin is currently the only antibiotic to have shown noninferiority to vancomycin in the treatment of MRSA bacteremia. Daptomycin resistance and cross-resistance in the setting of reduced vancomycin susceptibility raises concerns about widespread use of this agent. This may in part be explained by initial inadequate dosing. Two retrospective cohort studies indicate a possible advantage of daptomycin over vancomycin in infections caused by elevated vancomycin MIC. The results of an open-labeled trial to address this question are thus eagerly anticipated.

No drug till date has shown superiority to vancomycin in the treatment of MRSA infections with the possible exception of linezolid in HAP. As discussed, the absence of a mortality benefit despite increased clinical cure has led to much debate. Nevertheless, on balance linezolid should always be considered an option in the treatment MRSA-proven HAP. Whether these strengths and features are agent or class specific are unclear but will likely be answered with the marketing of tedizolid.

Although QD has good in vitro activity against MRSA, there are insufficient data to recommend its use as a first-line agent. In addition, administration issues (the requirement of a central line) and the significant adverse effects further impacts its possible role, as either salvage therapy or as an alternative in patients with multiple drug allergies. Similarly, tigecycline cannot be recommended as first-line therapy in serious MRSA infections.

In conclusion, there has been a welcome increase in the number of agents available for the treatment of MRSA. The exact role and choice of agent needs to be defined. Hopefully, this will not take as long as it has taken us to determine the optimal vancomycin dosing strategy.

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