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Site of infection rather than vancomycin MIC predicts vancomycin treatment failure in methicillin-resistant *Staphylococcus aureus* bacteraemia

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Background: Therapeutic use of vancomycin is characterized by decreased susceptibilities and increasing reports of clinical failures. Few studies have examined the clinical outcomes of patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia treated with vancomycin. The primary objective was to compare clinical outcomes of patients with MRSA bacteraemia treated according to standard of care practices.

Methods: Patients were included if: (i) admitted to University of New Mexico Hospital between 2002 and 2009; (ii) ≥18 years of age; (iii) had one blood culture positive for MRSA; and (iv) received vancomycin. Clinical outcomes were defined as cure, failure (relapse of infection 30 days after completion of therapy, death or change in therapy) or unevaluable. Patient demographics, source of bacteraemia, treatment regimen, and microbiological characteristics were determined.

Results: Two hundred patients with MRSA bacteraemia were included. Sixty-one patients were unevaluable, leaving 139 patients for the final analysis. Seventy-two (51.8%) patients were cured and 67 (48.2%) experienced vancomycin failure. Vancomycin MIC_{90} was 2 mg/L for both groups by Etest. Patients with endocarditis ($P=0.02$) or pneumonia ($P=0.02$) were more likely to fail therapy. Panton–Valentine leucocidin, loss of *agr* functionality and strain type were not predictors of outcomes in this study.

Conclusions: High failure rates were observed in patients with MRSA bacteraemia treated with vancomycin, despite high vancomycin troughs and low rates of nephrotoxicity. Predictors of vancomycin failure included endocarditis and pneumonia. In these situations, vancomycin provides suboptimal therapy.

Keywords: endocarditis, pneumonia, MRSA

Introduction

For over 30 years, vancomycin has been the mainstay of therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) infections, including bacteraemias, endocarditis and osteomyelitis.[1] Although resistance to vancomycin developed more slowly compared with other antibiotics, such as penicillin, its clinical use has become increasingly challenged as reports of resistant isolates and clinical failures become more prevalent.[2–4] In some situations, treatment failures have been associated with increasing vancomycin MICs, with worse clinical outcomes observed with MICs ≥2 mg/L. However, this finding has not been entirely consistent, with a few reports demonstrating a paradoxical effect in which isolates with higher MICs are less virulent and associated with decreased mortality.[3,5–9] Similarly, reports of VanA-mediated glycopeptide resistance, including vancomycin-intermediate *S. aureus* (VISA), heteroresistant VISA (hVISA) and even vancomycin-resistant *S. aureus* (VRSA) strains, have been reported to contribute to prolonged therapy, but no difference in mortality between these strains and vancomycin-susceptible MRSA strains were found.[10–12]

In addition to MICs, several *S. aureus* genotype markers have been proposed as possible mechanisms related to glycopeptide resistance and may serve as predictors of vancomycin failures. The accessory gene regulator (*agr*) operon is, through a quorum-sensing mechanism, known to be involved in regulating different virulence pathways, positively influencing the secretion of haemolysins and exotoxins and negatively influencing biofilm

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formation and the production of cell-associated virulence factors.[13] The loss of *agr* function has been associated with prolonged bacteraemia and an increased propensity towards the development of VISA and hVISA strains and vancomycin tolerance.[13–15]

The expression of Panton–Valentine leucocidin (PVL) correlates with a pore-forming exotoxin that targets polymorphonuclear leucocytes (PMNL), leading to PMNL lysis or apoptosis. It has largely been associated with community-acquired MRSA infections, but its presence is thought to confer more severe clinical sequelae, including leucopenia, sepsis and death.[16,17]

In 2009, the Infectious Diseases Society of America recommended high-dose vancomycin, targeting vancomycin serum trough concentrations of 15–20 mg/L for MRSA bacteraemias, to increase efficacy and improve clinical outcomes.[18] Similarly, optimizing the pharmacokinetics of vancomycin to achieve an AUC to MIC ratio ≥400 has been shown to predict more favourable microbiological and clinical outcomes in cases of *S. aureus* pneumonia.[19,20] However, this pharmacokinetic target has never been validated in cases of bacteraemia and the use of the higher vancomycin doses required to achieve these trough concentrations has been linked to nephrotoxicity, which further limits the clinical utility of vancomycin.[21–23] Few alternatives to vancomycin exist for treating serious or deep-seated MRSA infections and each has its own clinical limitations. Furthermore, in bacteraemias no alternative has ever been shown to perform better than vancomycin in a randomized clinical trial setting. Therefore, vancomycin has remained the standard of care unless patients fail therapy or cannot tolerate therapy due to adverse effects.[24]

At the University of New Mexico Hospital (UNMH), *S. aureus* susceptibility rates to vancomycin remain high (99.9%), yet an apparent increase in clinical failures has been observed in patients treated with vancomycin. To investigate this observation, this study was designed to evaluate factors associated with clinical outcomes of patients with vancomycin-susceptible MRSA bacteraemia treated with vancomycin. Secondary objectives were to compare patients who experienced a cure with those who failed vancomycin with respect to microbiological characteristics of MRSA, including loss of *agr* functionality, PVL, strain type and adverse drug reactions.

Methods

Data collection

A retrospective cohort study was conducted at UNMH, a 535 bed tertiary care academic medical centre. Patients were eligible for inclusion if they: (i) were admitted to UNMH between January 2002 and December 2009; (ii) were ≥18 years of age at the time of admission; (iii) had at least one blood culture positive for MRSA; and (iv) received treatment with vancomycin. Patients with multiple blood cultures for MRSA were included once, using their first blood cultures as the index case. If patients were readmitted >30 days after the end of their initial therapy, they were included for review provided the clinical outcome from their index case was not considered a failure. Patients with microbiological cultures positive for Gram-negative organisms were included if they received antibiotic therapy to which the organism was susceptible. Patients were excluded from review if they received initial therapy with linezolid or daptomycin. This study was approved by the University of New Mexico Human Research Review Committee.

Microbiological data from the reference laboratory were used to identify patients with MRSA bacteraemia who met the inclusion criteria. Data were retrospectively collected from patient medical charts using a systematic data collection form. Data elements included patient age, gender, race, height, weight, admission date, discharge date or date of death, and diagnosis. Co-morbid conditions, including diabetes mellitus, cancer, liver disease, end-stage renal disease, congestive heart failure, HIV infection, chronic lung disease and alcoholism were documented. The presence of shock, surgery or trauma upon admission was also documented. The severity of illness, described by the modified McCabe–Jackson scoring system, was used to categorize patients based on their underlying disease state as having non-fatal (life expectancy ≥5 years), ultimately fatal (death expected within a period of >3 months but <5 years) or rapidly fatal (death expected within 3 months) conditions at hospital admission. Risk factors for MRSA infection were recorded and defined as immunosuppression (treatment with >10 mg of prednisone or equivalent per day for >14 days prior to onset of infection, neutropenia, HIV, chemotherapy within 45 days before hospital admission and patients on immunosuppressive medications); previous healthcare exposure (home intravenous antibiotics or infusion clinic attendance 30 days prior to infection, hospital admission for ≥2 days within the past 90 days, haemodialysis 30 days prior to infection or resident of nursing home or long-term care facility); injection drug use; haemodialysis; prior antimicrobial exposure of duration ≥7 days within the last 30 days, including β-lactams, quinolones or vancomycin; presence of a central venous catheter, skin ulcers or cellulitis at admission; homelessness; and prior history of an MRSA infection or known MRSA carrier. Length of intensive care unit stay was also documented.

Data on all microbiological cultures, including date, source, pathogen and antibiotic susceptibilities, were recorded. Treatment course, comprising the drug, dose, frequency and duration for all antimicrobials, and appropriateness of therapy were documented. Concurrent antibiotics with *in vitro* activity against MRSA (e.g. clindamycin, doxycycline or sulfamethoxazole/trimethoprim) were recorded if administered for >48 h. Appropriate antimicrobial therapy was defined as initiation of at least one antimicrobial to which the bacterium was susceptible *in vitro* within the first 48 h of collection of the index blood culture. Initial and average vancomycin troughs during the course of therapy were documented. Sources of bacteraemia were determined from cultures other than blood, progress notes and clinical infectious diseases notes, and were categorized as infective endocarditis, osteomyelitis, skin and soft tissue infection, catheter-related bloodstream infection (including haemodialysis catheters), urinary tract infection, pneumonia, prosthesis or other. Sources of bacteraemia of unknown origin or sources not described by one of the previous categories were classified as other. Repeat blood cultures, if obtained, were used to document microbiological eradication or persistence of MRSA in the blood. Nephrotoxicity was defined as an increase in serum creatinine of ≥0.5 mg/dL or a 50% increase from baseline.

Clinical outcomes

Definitions for clinical outcomes were adapted from clinical studies of adult patients with serious MRSA infections.[20,21,25] Patient outcomes were categorized as cure, failure or non-evaluable based on information documented in the medical chart. Patients were considered to have a cure if their clinical signs and symptoms of infection had resolved and/or no additional antibiotic therapy was necessary. Microbiological eradication, as evidenced by negative blood cultures at the end of therapy, would also indicate therapeutic cure if blood cultures were obtained. Therapeutic failures were defined as an inadequate response to initial therapy requiring a change in antibiotic, relapse of infection at any body site within 30 days after the end of therapy, persistent bacteraemia (MRSA blood cultures ≥5 days after initiation of therapy), treatment-limiting adverse event or death

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during the treatment period. Patients for whom information was insufficient to determine a clinical outcome were classified as unevaluable. Patients were considered unevaluable if they had no follow-up at UNMH, were placed on chronic suppressive antibiotic therapy, left against medical advice, lost intravenous access or had third-party payers (i.e. insurance) that dictated specific antibiotic therapy.

Microbiological characterization

MIC determination

Subcultures of all clinical MRSA isolates were collected from the reference laboratory at the time blood cultures were identified and stored at −80°C. Vancomycin MICs were determined using Etest (0.016–256 mg/L) (AB Biodisk, Solna, Sweden) methodology, following the manufacturer's instructions.[26]

Functionality of agr

The δ-haemolysin activity on sheep blood agar plates was used as a surrogate marker of *agr* operon functionality, as previously described.[27] Absence of δ-haemolysin expression was interpreted as loss of *agr* function. Isolates were incubated for 24 h and read independently by two different investigators who were blinded to clinical outcomes.

PVL identification

PVL-positive MRSA isolates were identified using real-time PCR as described by Johnsson *et al.*[28] with modifications to the forward and reverse primers. The modified primers were designed based on the published PVL sequences, as reported by Deurenberg *et al.*[29] All samples were run in duplicate and the results for each run were averaged.

PFGE

Individual *S. aureus* isolates were embedded in agarose and lysed *in situ*, and genomic DNA was digested with the restriction endonuclease SmaI. The restriction fragments were resolved into a pattern of discrete bands in a 1% SeaKem Gold agarose gel by switching the current direction starting at 2 s and finishing at 40 s, using a linear ramping factor and a total run time of 16.5 h. The DNA fragment patterns were visualized by ethidium bromide staining and analysed by a computerized gel imaging software program (GelCompar II V3.0).[30]

Statistical analysis

Descriptive statistics, including mean, standard deviations and confidence intervals, were derived for variables and compared by univariate statistical procedures. All statistical tests were two-tailed and differences were considered statistically significant for P values <0.05. A multivariate binary logistic regression was used to identify variables significantly associated with vancomycin cures and failures. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and PASW Statistics, version 18 (SPSS, Chicago, IL, USA).

Results

Two hundred patients with MRSA bacteraemia met the inclusion criteria. Clinical outcomes could not be determined for 61 patients (unevaluable): 43 patients did not follow-up at UNMH, 7 patients had therapy determined by a third-party payer, 6 left against medical advice, 3 were placed on chronic suppressive antibiotics and 2 lost intravenous access. The remaining 139 patients were included in the final analysis. Seventy-two (51.8%) patients experienced cure with vancomycin and 67 (48.2%) patients experienced vancomycin failure. There were

Table 1. Patient demographic data and co-morbidities and risk factors for MRSA

Characteristic	Vancomycin cure ($n=72$)	Vancomycin failure ($n=67$)	P value
Age, years (mean±SD)	47.7±14	52.2±16	0.09
Gender			0.65
male	52 (72.2%)	46 (68.7%)	
female	20 (27.8%)	21 (31.3%)	
Race			0.45
Caucasian	28 (38.9%)	21 (31.3%)	
African American	5 (6.9%)	5 (7.5%)	
Hispanic	31 (43.1%)	28 (41.8%)	
Asian	0	0	
American Indian	3 (4.2%)	9 (13.4%)	
unknown	5 (6.9%)	4 (6.0%)	
Co-morbid conditions			
diabetes	29 (40.3%)	24 (35.8%)	0.59
cancer	11 (15.3%)	13 (19.4%)	0.52
liver disease	18 (25.0%)	21 (31.3%)	0.41
ESRD	9 (12.5%)	12 (17.9%)	0.38
CHF	6 (8.3%)	12 (17.9%)	0.10
HIV positive	6 (8.3%)	3 (4.5%)	0.36
chronic lung disease	3 (4.2%)	5 (7.5%)	0.41
alcoholism	8 (11.1%)	12 (17.9%)	0.26
shock at admission	4 (5.6%)	13 (19.4%)	0.02
surgery or trauma at admission	2 (2.8%)	4 (6.0%)	0.37
McCabe–Jackson score			<0.001
non-fatal	47 (65.3%)	29 (43.3%)	
ultimately fatal	25 (34.7%)	30 (44.8%)	
rapidly fatal	0	8 (11.9%)	
MRSA risk factors			
immunosuppression	11 (15.3%)	6 (9.0%)	0.26
previous healthcare exposure	28 (38.9%)	35 (52.2%)	0.12
injection drug use	18 (25.0%)	14 (20.9%)	0.57
haemodialysis	9 (12.5%)	10 (14.9%)	0.68
prior β-lactam use	2 (2.8%)	4 (6.0%)	0.37
prior quinolone use	5 (6.9%)	7 (10.4%)	0.47
prior vancomycin use	2 (2.8%)	3 (4.5%)	0.59
central venous catheter	11 (15.3%)	8 (11.9%)	0.57
skin ulcers on admission	8 (11.1%)	5 (7.5%)	0.46
cellulitis on admission	15 (20.8%)	7 (10.4%)	0.10
MRSA carrier (nares positive)	14 (19.4%)	8 (11.9%)	0.23
homeless	4 (5.6%)	5 (7.5%)	0.65

ESRD, end-stage renal disease; CHF, congestive heart failure.

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42 (30.2%) patients who died, 18 (12.9%) required a change in antibiotic therapy and 7 (5%) had a relapse of infection.

A comparison of patient demographics, co-morbidities and risk factors for MRSA infection showed no significant differences between the two groups, as shown in Table 1. However, McCabe–Jackson scores and shock on admission were statistically different between the two groups. A source of bacteraemia was identified in 70.8% of patients experiencing cure and 74.6% of patients who failed vancomycin. Transthoracic or transoesophageal echocardiograms were obtained in 44 (61.1%) and 30 (44.8%) patients with vancomycin cure and failure, respectively. Figure 1 shows the percentage of patients who achieved cure with vancomycin compared with those who failed according to the source of bacteraemia. Other sources of bacteraemia in patients cured with vancomycin included deep abscess ($n=5$), septic emboli to lungs ($n=6$), septic joints ($n=3$), unknown ($n=5$) and one case each of neutropenia and vein grafting. Similarly, other sources of bacteraemia in patients who failed vancomycin included septic emboli to the lungs ($n=4$), meningitis ($n=2$), unknown ($n=8$) and one case each of aplastic anaemia, trauma and deep abscess. Patients with endocarditis ($P=0.02$) or pneumonia ($P=0.02$) as the source of bacteraemia were more likely to fail vancomycin therapy when compared with patients with other sources of bacteraemia.

Table 2 lists the microbiological and therapeutic variables associated with vancomycin outcome. The vancomycin MIC_{90} was 2 mg/L for both groups by Etest. Figures 2 and 3 illustrate clinical outcome by vancomycin MIC and vancomycin MIC by primary source of bacteraemia. Functionality of *agr* and presence of the PVL gene were not significantly associated with any particular source of infection and did not significantly impact clinical outcomes. The predominant PFGE strain found among all MRSA isolates was USA300 (77/139, 55.4%) followed by USA100 (53/139, 38.1%). MRSA strains USA200 (5/139, 3.6%), USA500 (1/139, 0.7%) and USA1200 (2/139, 1.4%) were isolated less frequently. MRSA strain types were not significantly associated with any particular source of infection ($P=0.56$) or with vancomycin outcomes ($P=0.13$).

Vancomycin serum trough concentrations were available for 61 (84.7%) patients who were cured and 53 (79.1%) patients who failed therapy. Initial vancomycin troughs were not significantly different between the groups, but mean vancomycin troughs were significantly higher for those who failed therapy ($P=0.002$). Forty-two patients died while receiving vancomycin therapy, the average time to death being 13.2 ± 13.8 days.

Additional antibiotics with antistaphylococcal activity, such as doxycycline, clindamycin and sulfamethoxazole/trimethoprim, were analysed to see if their concomitant use provided vancomycin with any clinical advantage. No significant effect was observed.

A multivariate binary logistic regression was performed, controlling for age, gender and race, to examine which determinants were associated with vancomycin failures. Wald statistics, odds ratios and *P* values are reported in Table 3. Patients with endocarditis were three times more likely to experience vancomycin failure and patients with pneumonia were seven times more like to experience vancomycin failure compared with patients without these conditions. Receiver operator curves (ROC) were computed to further examine the sensitivity and specificity of endocarditis and pneumonia in relation to vancomycin outcomes.[31] Thirty-one per cent of the area under the ROC curve was accounted for when pneumonia was examined in relation to vancomycin failures ($P=0.04$, 95% confidence interval 0.17–0.47). In contrast, when endocarditis was examined in relation to vancomycin failures the area under the ROC curve was not significant ($P>0.05$). The large odds ratio and significant

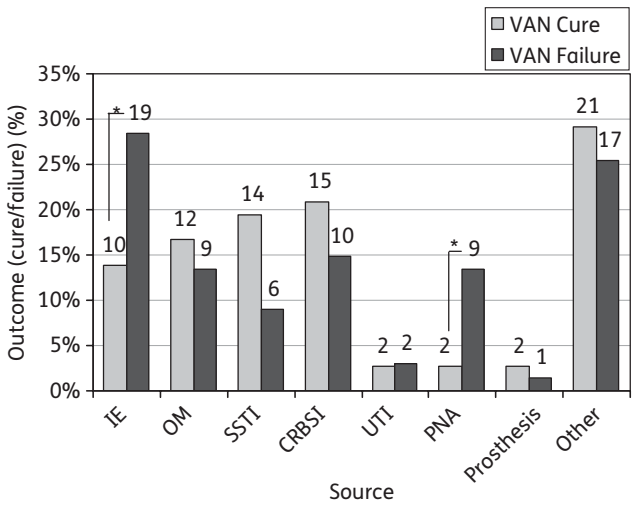

Figure 1. Clinical outcomes by source of bacteraemia. *$P<0.02$. VAN, vancomycin; IE, infective endocarditis; OM, osteomyelitis; SSTI, skin and soft tissue infection; CRBSI, catheter-related bloodstream infection (including haemodialysis catheters); UTI, urinary tract infection; PNA, pneumonia.

Table 2. Microbiological and therapeutic characteristics of MRSA bacteraemia

Microbiological and therapeutic characteristics	Vancomycin cure ($n=72$)	Vancomycin failure ($n=67$)	*P* value
Appropriate therapy	60 (83.3%)	56 (83.6%)	0.97
MIC_{90} (range), mg/L	2 (0.75–3)	2 (1–4)	0.20
PVL positive	41 (56.9%)	33 (49.3%)	0.36
Loss of *agr* functionality	13 (18.1%)	13 (19.4%)	0.84
Initial vancomycin trough ± SD, mg/L	11.3 ± 0.77	13.8 ± 1.06	0.06
Mean vancomycin trough ± SD, mg/L	15.6 ± 6.1	21.4 ± 12.6	0.002
Patients with persistent blood cultures	2 (2.8%)	8 (11.9%)	0.04
Patients requiring ICU care	18 (25.0%)	36 (53.7%)	<0.0001
ICU length of stay, days	3.7 ± 1.3	6.4 ± 1.2	0.17
Concomitant use of antibiotics >48 h			
doxycycline	2 (2.8%)	6 (9.0%)	0.12
clindamycin	10 (13.9%)	5 (7.5%)	0.22
sulfamethoxazole/trimethoprim	8 (11.1%)	4 (6.0%)	0.28

ICU, intensive care unit.

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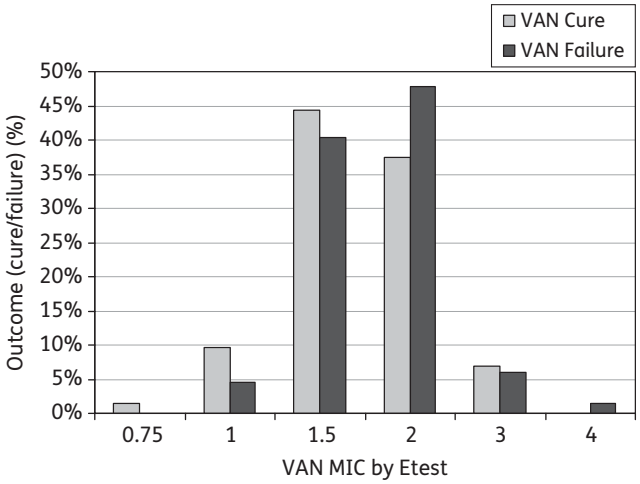

Figure 2. Clinical outcome by vancomycin MIC (mg/L). VAN, vancomycin.

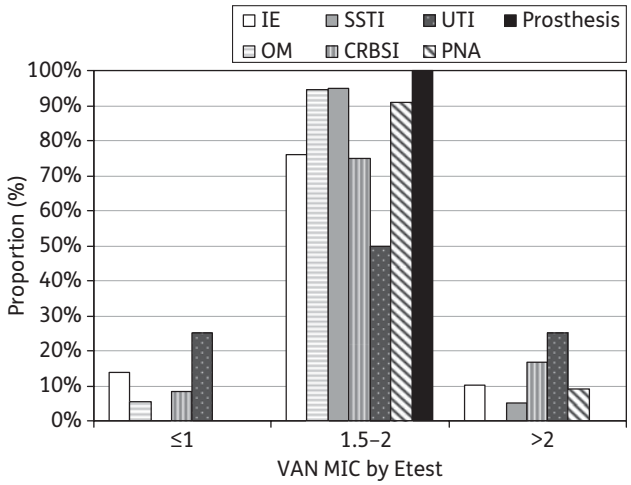

Figure 3. Vancomycin MIC (mg/L) by primary source of bacteraemia. VAN, vancomycin; IE, infective endocarditis; OM, osteomyelitis; SSTI, skin and soft tissue infection; CRBSI, catheter-related bloodstream infection (including haemodialysis catheters); UTI, urinary tract infection; PNA, pneumonia.

area accounted for in the ROC curve lends credence to pneumonia being a strong determinant of vancomycin failures.

Nephrotoxicity was the most common adverse event experienced by patients; it occurred in 8 patients who experienced cure and 20 patients who failed therapy. Each group had an equal proportion of patients with diabetes, exposure to aminoglycosides and intravenous contrast agent administration used in diagnostic imaging studies; however, there were more patients with endocarditis and nephrotoxicity (6/19, 31.6%) who failed vancomycin compared with those who experienced cure (1/10, 10%). Seven patients were classified as vancomycin failure as a result of nephrotoxicity, meaning that vancomycin was changed to an alternative antibiotic to complete their course of therapy. In a subanalysis, initial and mean vancomycin troughs for these patients were 16.5 ± 3.1 mg/L and 22.7 ± 3.6 mg/L, respectively. No apparent correlation between vancomycin troughs and nephrotoxicity was observed in this study. In addition to nephrotoxicity, two patients developed a rash and one patient developed drug fever, leucopenia and diarrhoea that resulted in discontinuation of vancomycin and substitution of an alternative agent to complete the duration of therapy.

Table 3. Multivariate analysis of factors associated with vancomycin failures

Predictor	Wald	*P* value	Odds ratio	95% confidence interval
Age	4.22	0.04	1.03	1.0–1.05
Gender	0.41	0.52	0.76	0.33–1.74
Race	2.94	0.57	—	—
Endocarditis	5.61	0.02	3.12	1.22–8.21
Pneumonia	5.18	0.02	7.25	1.31–39.9
Osteomyelitis	0.05	0.81	0.89	0.31–2.48
Vancomycin Etest	3.90	0.56	—	—

Discussion

In this study, almost half of the patients with MRSA bacteraemia treated with vancomycin ultimately failed therapy, despite having vancomycin MICs within the susceptible range. Predictors of vancomycin failures included endocarditis and pneumonia as the source of bacteraemia. Furthermore, optimization of the vancomycin dose to target higher serum troughs did not improve clinical outcomes.

Our results highlight the importance of the underlying disease state and severity of disease rather than vancomycin MICs in predicting vancomycin failures. These results are similar to those of Lalueza *et al.*,[9] who examined mortality among patients with MRSA bacteraemia according to vancomycin MIC and found no difference in outcomes. Other studies have likewise found associations between disease state and clinical failures; however, these results were attributed to elevated vancomycin MICs, which was not the case in our study. Lodise *et al.*[3] also found a significant association between endocarditis and treatment failure, but overall failure was attributed to elevated MICs. Soriano *et al.*[5] found that prognosis of the underlying disease (McCabe–Jackson score) and source of bacteraemia were independently associated with increased mortality, as well as MICs >2 mg/L. Of note, these studies show worse clinical outcomes despite vancomycin MICs within the susceptible range, which raises the question of whether vancomycin MICs are reliable predictors of clinical outcomes.

It is plausible that the pharmacokinetics of vancomycin combined with its pharmacodynamic effects on specific disease states are preventing vancomycin from achieving appreciable concentrations at the site of infection to optimize its bactericidal effects on MRSA infections. In a pharmacokinetic model of high-dose vancomycin for treatment of pneumonia using epithelial lining fluid penetration of 100%, vancomycin concentrations were not sufficient to provide the optimal exposure necessary to achieve bactericidal effects.[32] Another pharmacokinetic study suggests that disease states associated with high bacterial

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inoculums, such as endocarditis or infections involving a prosthesis, were more likely to demonstrate reduced vancomycin efficacy, with little or no decrease in the inoculum size, while selecting for isolates with higher MICs.[33] These data may further explain why increasing the dose to achieve higher serum trough concentrations, to maximize the AUC to MIC ratio, does not necessarily correlate with improved outcomes.[3,6,22]

In our study, MRSA virulence factors, including loss of *agr* function and presence of the PVL gene, did not significantly impact clinical outcomes. These results are similar to observations by Lalani *et al*.,[34] who collected MRSA bloodstream isolates as part of a multinational Phase III clinical trial and found no association between virulence factors, including *agr* and clinical outcomes. Price *et al*.[35] also looked at *S. aureus* bacteraemia isolates over time and found no association between complicated disease and the presence of the PVL gene. Our findings reflect the limited clonal variation present in our patient population, which may have hindered our ability to detect a significant correlation with disease state.

Limitations

This was a single-centre, non-randomized, retrospective study with inherent limitations. However, this study represents the standard of care at most institutions. We included patients with secondary infections in addition to MRSA bacteraemia, which may have adversely impacted clinical outcomes. While vancomycin troughs did not correlate with nephrotoxicity, patients on vancomycin were closely monitored for both efficacy and toxicity and dosing was adjusted based on individual patient pharmacokinetic parameters as opposed to a nomogram. In addition, our rates of endocarditis may be underestimated since not all patients received an echocardiogram to evaluate for disseminated disease.

Conclusions

Our study demonstrates that MRSA bacteraemias treated with vancomycin are associated with high failure rates despite MICs being within the susceptible range. Furthermore, optimization of vancomycin therapy to achieve a higher serum trough concentration did not improve clinical outcomes. Although MICs provide clinicians with a relative assumption about clinical outcomes, MICs need to be interpreted within the context of the clinical picture. Characteristics of the disease state, including site of infection and severity, ultimately determine whether the pharmacokinetic and pharmacodynamic parameters of vancomycin relative to the MIC can be attained without causing undue harm to the patient. In the case of MRSA bacteraemia due to endocarditis or pneumonia, vancomycin provides suboptimal therapy. More studies comparing the performance of alternative therapies with that of vancomycin in serious MRSA infections such as pneumonia and bacteraemia are needed.

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Transparency declarations

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