Impact of source of infection and vancomycin AUC_{0-24}/MIC_{BMD} targets on treatment failure in patients with methicillin-resistant *Staphylococcus aureus* bacteraemia

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Abstract

Despite recent controversies about toxicity and reduced efficacy, vancomycin remains the current treatment of choice for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia. The parameter associated with treatment success is the vancomycin 24-h area under concentration-time curve to MIC ratio (AUC_{0-24}/MIC). We aimed to determine the utility of calculated AUCs and explore the optimal AUC_{0-24}/MIC targets associated with treatment success. In this single-centre retrospective observational cohort study of 127 patients with MRSA bacteraemia, forty-five (35.4%) did not respond to vancomycin treatment. Patient characteristics were essentially the same between those who did not respond to vancomycin treatment and those with treatment success, with independent predictors of treatment failure being source of bacteraemia (odds ratio (OR), 4.29; 95% confidence interval (CI), 1.50–12.26; p 0.007) and not achieving an AUC_{0-24}/MIC_{BMD} (using broth microdilution) target of $\geq$398 (OR, 11.4; 95% CI, 4.57–28.46; p< 0.001). Bacteraemic source-specific thresholds were observed with a higher AUC_{0-24}/MIC_{BMD} target of 440 required for high-risk sources (e.g. infective endocarditis) compared with 330 for low-risk sources (line related bacteraemia). Overall treatment success in patients with MRSA bacteraemia was associated with a vancomycin AUC_{0-24}/MIC_{BMD} target of $\geq$398, with source-specific targets observed. Future vancomycin practice guidelines will need to take into account MIC methodology, source of bacteraemia and patient populations prior to setting targets and monitoring recommendations.

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia accounts for a high proportion of healthcare and community onset infections worldwide. These bacteraemic episodes in turn result in significant patient morbidity and mortality [1–3].

The mainstay of therapy remains vancomycin despite controversies about efficacy and potential toxicity [4]. Glycopeptides including vancomycin exhibit concentration-independent killing, with the pharmacodynamic parameter best associated with efficacy being the ratio of the 24-h area under the concentration-time curve to minimum inhibitory concentration (AUC_{0-24}/MIC) [5,6]. Using broth microdilution (BMD), initial AUC_{0-24}/MIC thresholds of 866 and 345 for bacterial eradication and clinical success, respectively, were observed following an *S. aureus* pneumonia study [7]. In light of these results and animal infection model data consensus guidelines recommended a vancomycin AUC_{0-24}/MIC target of $\geq$400 for serious MRSA infections [8]. Subsequently, similar targets using classification regression tree (CART) analysis have been

observed in MRSA bacteraemia studies [9–12]. Although slight differences in the targets exist this is largely explained by the MIC methodology employed, with AUC$_{0-24}$/MIC$_{Etest}$ targets between 214 and 293 [9–11] compared with AUC$_{0-24}$/MIC$_{BMD}$ targets between 373 and 421 [11,12].

Notwithstanding these vancomycin exposure targets, guidelines published in 2009 continue to recommend monitoring of steady state trough concentrations and suggest aiming for levels between 15 and 20 mg/L for serious infections [8]. This recommendation was partly based on modelling, which showed appropriate target attainment provided isolates had MICs ≤1 mg/L and the availability of trough measurements in routine diagnostic laboratories [7,13,14]. Consequently, to assist clinicians in achieving recommended vancomycin troughs, several nomograms have been validated and published [15].

Two recent controversies, however, have challenged vancomycin dosing based on trough concentrations. On the one hand, increased mortality and treatment failures are observed with high vancomycin MIC MRSA infections [4,16]. On the other hand, more aggressive dosing leads to a greater chance of renal injury [17]. Both these concerns argue for dosing aimed at PK/PD targets, which would optimize individual patient exposure and at the same time minimize renal injury. Several methods exist for determining vancomycin AUCs. These include deriving vancomycin AUC from validated formulae, population models or Bayesian estimations. Although each has its own advantages and disadvantages, the latter two methods currently are unlikely to become routine, as they require appropriate infrastructure, frequent sampling and highly skilled staff to be implemented [18].

We undertook this study to evaluate the utility of previously validated AUC predictions (based on creatinine clearance estimation) and explore the optimal AUC$_{0-24}$/MIC targets for vancomycin in patients with MRSA bacteraemia and whether observed targets are influenced by sources of bacteraemia.

Methods

Study population

Following institutional ethics approval, all adult patients (>18 years) admitted with MRSA bacteraemia to Liverpool Hospital between January 2006 and January 2012 were screened for inclusion in this retrospective observational cohort study. Patients were included if they met the following criteria: they received ≥7 days of vancomycin monotherapy following MRSA bacteraemia diagnosis and had an actual weight recorded in the medical record. Patients with chronic renal impairment requiring dialysis prior to admission were

excluded from the study, as clearance calculations are less robust in these patients. In patients with multiple MRSA bacteraemic episodes over the period only the first episode was included in the study.

Data collection

Data for age, sex, source of bacteraemia and weight were collected following a detailed review of the medical records. Similarly, all co-morbidities were collated and used to calculate the Charlson weighted index for each individual patient. The APACHE II score was used as a marker of illness severity and was calculated based on the worst physiological parameters within the first 48 h following the positive MRSA blood culture bottle [19]. Administered vancomycin doses, including loading doses if prescribed, for each patient were confirmed using our pharmacy-dispensing database. Vancomycin troughs (obtained a minimum of 12 h after the last dose) were obtained from the biochemistry data and correlated with date and timing of vancomycin to ensure steady state trough concentration.

Microbiology

In all patients, including patients with persistent bacteraemia, only the first positive blood culture isolate was used for MIC determination. All isolates were retrieved from −80°C storage and subcultured on horse blood agar (HBA) twice prior to testing. Etest (0.016–256 mg/L; AB bioMerieux, Solna, Sweden) vancomycin MICs were determined according to the manufacturer's instructions. In addition, broth microdilution (BMD) was performed on all isolates as per the Clinical and Laboratory Standard Institute (CLSI) methodology [20], inclusive of an additional 1.5 mg/L concentration step. Heteroresistant vancomycin intermediate *S. aureus* (hVISA) testing was not performed.

Vancomycin pharmacokinetic/pharmacodynamic data

Vancomycin AUC was calculated using a validated formula [7] based on previously established vancomycin pharmacokinetics [21], where the estimated AUC equals the total vancomycin dose in mg over 24 h/([(creatinine clearance × 0.79) + 15.4] × 0.06). As in the original study, creatinine clearance (CL$_{CR}$) was estimated using the Cockcroft-Gault equation; that is, CL$_{CR}$ = {[(140 − age in years) × recorded actual body weight in kg]/(serum creatinine in μM × 0.814)} or × 0.85 if female [22]. For overweight patients (weight >100 kg) adjusted body weight (which equates to ideal body weight + 0.4 × (actual − ideal body weight)) was used to calculate the CL$_{CR}$. AUCs were calculated using the total vancomycin dose, which corresponded with dosing at steady state conditions (between 72 and 96 h). Calculations were not dependant on subsequent clinician-directed dosage changes

based on obtained trough levels. Both MIC methodology results were used to examine AUC_{0-24}/MIC targets.

Definitions

The source of bloodstream infections (BSIs) was classified as previously described [23] into three categories: low-risk sources (related mortality <10%), which included intravenous catheter, urinary tract, ear-nose-larynx and gynaecological sources; intermediate-risk sources (associated mortality between 10 and 20%), which included osteo-articular sources, soft tissue and unknown sources; and high-risk sources (associated mortality >20%), which included endovascular sources, pneumonia, abdominal sources and central nervous system foci.

Outcomes

Similarly to previous studies a composite endpoint comprising all current aspects considered as treatment failure was chosen [12,24]. Following chart review by the authors, vancomycin treatment failure was defined as any one of the following: (i) 30-day overall mortality; (ii) persistent bacteraemia ≥7 days; or (iii) microbiological failure (i.e. MRSA isolation from a sterile site) with persistent signs and symptoms of MRSA infection following 14 days of vancomycin [12,24].

Statistical analysis

Categorical variables were compared using the χ^2 test or Fishers exact test, and continuous variables compared by the Students *t*-test or Mann–Whitney *U*-test Classification and Regression Tree (CART) analysis (which uses decision tree algorithms to determine the best if-then split conditions that accurately predict an outcome of interest) was used to identify overall and source-specific AUC/MIC targets for treatment failure. A p value of <0.05 was considered significant. Multivariable backward stepwise logistic regression analysis was performed to identify predictors of treatment failure. All variables with a p value <0.2 and those previously identified to be associated with outcome (e.g. elevated vancomycin $MIC_{E\ test}$, APACHE II score and CWI) were included in the model *a priori* with the goodness of fit of the final model assessed using the Hosmer-Lemeshow statistic. All calculations were computed using SPSS (version 22.0) and CART software (Salford Predictive Modeler version 7; Salford Systems, San Diego, CA, USA).

Results

Demographics

During the study period 199 MRSA episodes were identified. Of these, 127 patients were included in the study, with patients excluded for the following reasons: missing clinical data (*n* = 9); chronic renal impairment requiring dialysis (*n* = 27); no stored isolate (*n* = 2); not treated, treated with combination or alternative therapy (*n* = 32); and recurrent episodes (*n* = 2).

The median age was 64.6 years (range 22–95) and there was a predominance of male patients (68.5%). All patients had at least two co-morbidities with a median APACHE II score of 11 (range 0–37). The majority of episodes occurred in hospital (52.0%), with line-related bacteraemia being the most common source (26.7%) of bacteraemia. Infective endocarditis (*n* = 12), pneumonia (*n* = 19), abdominal sources (*n* = 6) and non-endocarditis vascular sources (*n* = 2) made up all high-risk episodes and together accounted for 30.7% of all episodes.

Susceptibility testing

The isolates' MIC distribution by methodology is displayed in Table 1, with a significant difference observed between Etest results (MIC_{90} = 2 mg/L) and broth microdilution (MIC_{90} = 1 mg/L) (Spearman's rho = 0.398; p< 0.01).

Vancomycin trough levels

The median intravenous vancomycin dose at steady state was 2000 mg/day (range 500–4000 mg/day) administered over 2–4 h, which resulted in a median trough level of 13.1 mg/L (range 3.5–35.7 mg/L) based on a single patient's result taken at steady state. Depending on bacteraemia source, patients were treated with intravenous therapy for between 2 and 6 weeks; no combination therapy was prescribed in any episodes. Oral step-down therapy with rifampicin and fusidic acid was employed predominantly in patients with bone and joint infections and only occurred following completion of intravenous antibiotics.

Renal clearance and vancomycin AUC_{0-24}

The median weight was 70 kg (range 39–184 kg), with 9.4% (12/127) of patients weighing greater than 100 kg. Renal function was impaired at baseline secondary to the bacteraemia in 34.4% (44/128), with a median calculated creatinine

TABLE 1. Vancomycin inhibitory concentration testing results by methodology

Etest MIC (mg/L)	No of isolates with BMD MIC (mg/L)						
	0.25	0.5	1	1.5	2	4	Total
0.5	1	5	4	0	0	0	10
0.75	0	10	14	0	0	0	24
1	0	6	32	2	2	0	42
1.5	0	2	34	1	0	1	38
2	0	0	9	2	2	0	13
Total	1	23	93	5	4	1	127

clearance (Cockcroft-Gault equation) of 67. mL/min (range 11–191 mL/min). Only one patient had a supranormal (>130 mL/min) calculated creatinine clearance and not surprisingly this patient attained an AUC_{0-24}/MIC_{BMD} <400. The patient's MRSA bacteraemia was secondary to a line-related source with subsequent treatment failure (exit site abscess 21 days after commencement of vancomycin and line removal). None of our presented results changed when this patient was excluded.

A median calculated vancomycin AUC_{0-24}/MIC ratio of 448 mg*h/L (range 72–1906 mg*h/L) using BMD MIC results was obtained. Given the 1–2 dilution higher Etest MIC results compared with BMD, not surprisingly, the median vancomycin AUC_{0-24}/MIC ratio was significantly lower at 369 mg*h/L (range 88–1341 mg*h/L) when calculated using Etest results (p< 0.01).

Calculated AUC values (Spearman's rho = 0.756) correlated better with AUC_{0-24}/MIC_{BMD} values compared with vancomycin trough levels at 96 h (Spearman's rho = 0.301). Of patients achieving an appropriate AUC_{0-24}/MIC_{BMD} target of ≥400, 61% (47/77) had vancomycin troughs <15 mg/L and thus potentially would have their dosing increased, resulting in a possible increased risk of nephrotoxicity. Similarly, 34% (17/50) had trough levels between 15 and 20 mg/L but did not achieve the recommended target, resulting in 'under'-exposure (See Fig. 1).

Effect of AUC/MIC attainment on treatment failure

Forty-five patients (35.4%) had evidence of treatment failure: persistent bacteraemia (n = 11), microbiological failure (n = 12) and overall 30-day mortality (n = 22). Seven patients

met more than one category for treatment failure (See Table 2). Diagnosis of persistent bacteraemia occurred on average 12 and 10 days following the initial positive blood culture bottle and initiation of vancomycin. Microbiological failure was confirmed on average 20 days from the initiation of treatment and occurred predominantly (66.7%; 8/12) in patients who did not undergo definitive source control (e.g. device removal or abscess drainage). Not surprisingly, given the definitions, source of bacteraemia (i.e. high vs. intermediate/low risk sources) predicted overall 30-day mortality (p< 0.001) and persistent bacteraemia (p 0.044) but not microbiological failure (p 0.590) (Table 2).

Using CART, a significant AUC_{0-24}/MIC_{BMD} of 398 was detected: vancomycin failure occurred in 54% (27/50) of patients with AUC_{0-24}/MIC less than 398 compared with 23.4% (18/77) in patients with values greater or equal to 398 (p< 0.01). Similar results were seen with AUC_{0-24}/MIC_{Etest} but at a lower target of 270 (data not shown). Other variables associated with treatment failure included presence of chronic lung disease, receipt of immunosuppression at time of bacteraemia and high-risk sources (see Table 3). Although an elevated MIC by Etest was associated with higher rates of failure it did not reach statistical significance (p 0.137).

Independent predictors of treatment failure based on multivariable logistic regression (Table 4) included vancomycin AUC_{0-24}/MIC_{BMD} <398, high-risk bacteraemic sources and immunosuppression (Hosmer-Lemeshow statistic for the final model, chi-squared 1.2, p 0.882). AUC_{0-24}/MIC_{Etest} <270 was likewise an independent predictor of failure when included in the model in place of AUC_{0-24}/MIC_{BMD} (OR, 5.4; 95% CI, 2.0–14.7; p< 0.001).

FIG. 1. Scatterplot of measured vancomycin trough levels at steady state and vancomycin AUC_{0-24}/MIC_{BMD}. Lines represent recommended vancomycin trough targets on the *x*-axis and vancomycin AUC_{0-24}/MIC_{BMD} on the *y*-axis.
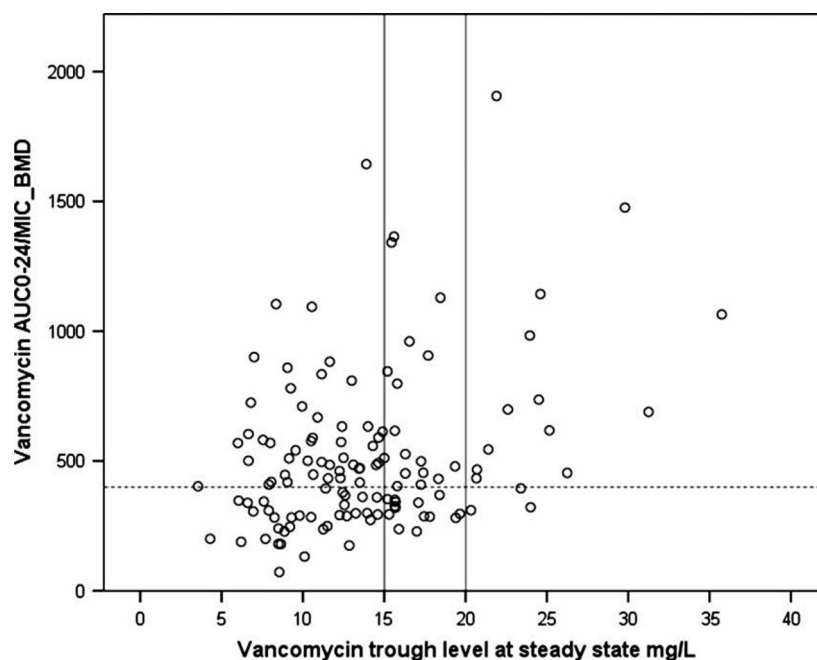
TABLE 2. Breakdown of treatment failure by prognostic source of bacteraemia

Characteristic	Number of events
Overall 30-day mortality	22
High-risk sources (*n* = 39)	16[a]
Intermediate sources (*n* = 50)	4
Low-risk sources (*n* = 38)	3
Persistent bacteraemia	11
High-risk sources (*n* = 39)	5 (5)[bc]
Intermediate sources (*n* = 50)	2 (2)[c]
Low-risk sources (*n* = 38)	4
Microbiological failure	12
High-risk sources (*n* = 39)	4[d]
Intermediate sources (*n* = 50)	6
Low-risk sources (*n* = 38)	2

Source of bacteraemia grouped into one of three groups based on overall mortality risk (see text for details).
Low risk: line-related bacteraemia (*n* = 35) and other sources (*n* = 3).
Intermediate risk: bone and joint (*n* = 14), skin and soft tissue infections (*n* = 20), deep abscess (*n* = 4), no identified focus (*n* = 12).
High risk: infective endocarditis (*n* = 12), pneumonia (*n* = 19), abdominal sources (*n* = 6) and non-endocarditis vascular sources (*n* = 2).
[a]High-risk sources were significantly more likely to result in overall mortality compared with intermediate/low-risk sources (p< 0.001).
[b]High-risk sources were significantly more likely to result in persistent bacteraemia compared with intermediate/low-risk sources (p 0.044).
[c]Numbers in the brackets represent additional patients who had persistent bacteraemia. These seven patients all died and thus were included in the analysis as a death only. No patients with microbiological failure died at 30 days or had persistent bacteraemia.
[d]Similar rates of microbiological failure were seen irrespective of source of bacteraemia (p 0.590).

Effect of bacteraemic source on AUC/MIC target

Source-specific AUC_{0-24}/MIC_{BMD} targets were identified using CART analysis: 440, 363 and 330 for high, intermediate and low-risk sources, respectively. The relationship between AUC_{0-24}/MIC_{BMD} values and treatment failure stratified by source of bacteraemia can be seen in Fig. 2. Patients achieving AUC_{0-24}/MIC_{BMD} values below identified targets were significantly more likely to experience treatment failures compared with patients achieving levels above the target (Fig. 3). The difference between AUC_{0-24}/MIC_{BMD} targets for intermediate and low risk sources, although small, was meaningful. When applying the lower target of 330 to intermediate sources, two less treatment failures (2/11; 18%) were identified. Specific bacteraemic diagnoses were not examined due to the low numbers of patients in each of the groups.

Discussion

There are several notable findings from our observational cohort study. First, vancomycin steady state trough concentrations correlated poorly with pharmacodynamic targets. This is not surprising as the denominator of the AUC_{0-24}/MIC_{BMD} equation has an exponential effect on the final result. Moreover, dosing adjustments based on vancomycin trough concentrations would have resulted in a considerable proportion of patients attaining AUC_{0-24}/MIC_{BMD} above or below recommended targets. Consequences of not attaining recommended targets include the possible emergence of vancomycin

TABLE 3. Patient demographics grouped by treatment outcome[a]

Characteristic	Treatment failure (*n* = 45)	Treatment success (*n* = 82)	p Value
Age ≥70 years	20 (44.4)	34 (41.5)	0.851
Male sex	29 (64.4)	58 (70.7)	0.550
Median weight in kg (range)	70 (40–110)	70 (39–184)	0.721
Co-morbidities			
Heart disease	10 (22.2)	18 (22.0)	0.972
Diabetes	14 (31.1)	28 (34.1)	0.844
Malignancy	15 (33.3)	21 (25.6)	0.624
Chronic liver disease	3 (6.7)	6 (7.3)	1.000
Chronic lung disease	9 (20.0)	6 (7.3)	0.034
Immunosupression	11 (24.4)	10 (12.2)	0.076
Charlson weighted index ≥3	19 (42.2)	34 (41.5)	0.934
Origin of bacteraemia			
Community onset	24 (53.3)	37 (45.1)	0.320
Hospital onset	21 (46.7)	45 (54.9)	
Location of bacteraemia			
Transit to or in ICU	14 (31.1)	19 (23.2)	0.577
Ward patient	31 (68.9)	63 (76.8)	
Severity of illness			
Median APACHE II score (range)	12 (2–37)	11 (0–30)	0.147
Median C-reactive protein in mg/L (range)	185 (6–410)	155 (10–430)	0.733
Median albumin in g/L (range)	31 (16–42)	30 (17–45)	0.978
Source of bacteraemia[b]			
Low risk	8 (17.8)	30 (36.6)	0.027
Intermediate risk	11 (24.4)	39 (47.6)	0.011
High risk	26 (57.8)	13 (15.9)	<0.001
Vancomycin Etest MIC >1 mg/L	22 (48.9)	29 (35.4)	0.137
Vancomycin AUC_{0-24}/MIC_{BMD} <398	27 (60.0)	23 (28.0)	0.001
Vancomycin trough at steady state <15 mg/L	21 (46.7)	26 (31.7)	0.095

ICU, intensive care unit; MIC, minimum inhibitory concentration; AUC, area under the concentration curve; BMD, broth microdilution; IQR, interquartile range.
Values expressed as numbers (%) unless otherwise stated.
Low risk: line-related bacteraemia (*n* = 35) and other sources (*n* = 3).
Intermediate risk: bone and joint (*n* = 14), skin and soft tissue infections (*n* = 20), deep abscess (*n* = 4), no identified focus (*n* = 12).
High risk: infective endocarditis (*n* = 12), pneumonia (*n* = 19), abdominal sources (*n* = 6) and non-endocarditis vascular sources (*n* = 2).
[a]Treatment failure defined as one of the following: persistent bacteraemia, microbiological failure or overall 30-day mortality (see text for details). Data presented in numbers of cases (%) unless stated.
[b]Source of bacteraemia grouped into one of three groups based on overall mortality risk (see text for details).

hetero-resistance with under-dosing [25] and increased risk of nephrotoxicity with increasing drug exposure [26]. Therefore, to optimize individual patient vancomycin exposure requires AUC_{0-24}/MIC_{BMD} monitoring. However, as opposed to vancomycin trough monitoring, AUC_{0-24}/MIC_{BMD} monitoring is more complex and relies on appropriate available expertise. Nevertheless, our data confirm the utility of using a published formula for AUC estimation as we observed a similar AUC_{0-24}/MIC_{BMD} target (of ≥398) associated with treatment success [9–12]. Second, required AUC_{0-24}/MIC targets are influenced by the source of bacteraemia, with higher targets required for treatment success in high-risk sources such as infective endocarditis compared with low-risk sources such as line-related bacteraemia.

Vancomycin treatment failure was predominantly observed in patients with high-risk bacteraemic sources. This
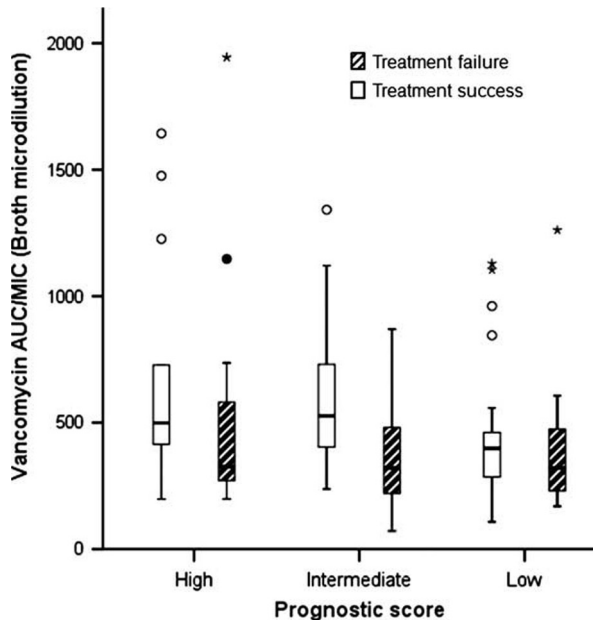
FIG. 2. Box plots for vancomycin AUC$_{0-24}$/MIC$_{BMD}$ values in patients experiencing treatment failure or success stratified by source of MRSA bacteraemia. Source of bacteraemia grouped into one of three groups based on overall mortality risk (see text for details). Median and interquartile AUC$_{0-24}$/MIC$_{BMD}$ values are represented by boxplots with whiskers representing minimum and maximum values. Circles represent outliers.

observation is not entirely unexpected as microbiological failure or persistent bacteraemia is commonly associated with high inoculum infections such as infective endocarditis [3,27]. Nevertheless, failure still occurred with all bacteraemic sources. Our data suggest that bacteraemic source or

infection-specific AUC$_{0-24}$/MIC$_{BMD}$ targets may exist. Although these findings require confirmation prior to introduction into clinical practice, we anticipate that AUC$_{0-24}$/MIC$_{BMD}$ targets for low-risk sources secondary to skin and soft tissue infections (SSTI) are lower than those required for high-risk MRSA bacteraemic sources to achieve similar cure rates.

It is clear from our study that optimized dosing in MRSA bacteraemia requires monitoring of both AUC$_{0-24}$ and MIC values. Alternatively, it can be inferred from our data that vancomycin trough monitoring may not be of benefit. However, this is not the case, with trough monitoring still the best indicator of possible nephrotoxicity [17]. Furthermore, original modelling data suggest that adequate pharmacodynamic targets are obtained when dosing is based on vancomycin trough concentrations provided MICs are ≤1 mg/L [8]. However, the level of accuracy with respect to the true attained AUC$_{0-24}$/MIC$_{BMD}$ at an individual patient level would be method dependent, with trough measurements the least accurate, and Bayesian modelling based on frequent sampling the most accurate. Which method should be employed at the bedside is unclear and is likely to vary with the clinical setting. For example, optimized therapy based on AUC/MIC monitoring may be more appropriate in critically ill patients, such as those in the intensive care unit, compared with ward patients with uncomplicated bacteraemia.

Clinicians should be cognizant, however, that the equation used is dependent on creatinine clearance (Cr$_{CL}$) estimations, which are likely to be an additional source of error. Unlike a recent study [11], we found that the method of determining Cr$_{CL}$ did affect the AUC/MIC result, with the Modified Diet in

FIG. 3. The proportion of patients not responding to vancomycin by source of bacteraemia when AUC$_{24}$/MIC$_{BMD}$ values were above and below CART-identified source-specific targets. Source of bacteraemia grouped into one of three groups based on overall mortality risk (see text for details).
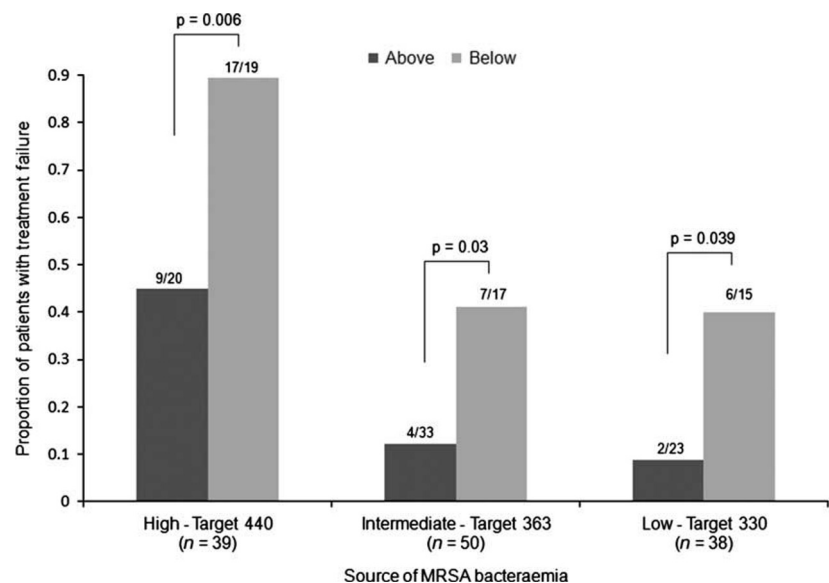
TABLE 4. Final multivariable logistic regression model of factors associated with treatment failure

Variable	Univariate analysis p value	Multivariable analysis[a]		
		OR	95% CI	p Value
Chronic lung disease	0.034			
Immunosuppression	0.076	3.45	1.07–11.3	0.038
Source of bacteraemia[b]				
Low risk	0.027			
Intermediate risk	0.011			
High risk	<0.001	11.1	4.0–30.4	<0.001
Vancomycin Etest MIC >1 mg/L	0.137			
Vancomycin AUC_{0-24}/MIC_{BMD} <398	0.001	7.23	2.7–19.5	<0.001
Vancomycin trough at steady state <15 mg/L	0.095			

Low risk: line-related bacteraemia ($n = 34$) and other sources ($n = 3$).
Intermediate risk: bone and joint ($n = 15$), skin and soft tissue infections ($n = 20$), deep abscess ($n = 4$), no identified focus ($n = 12$).
High risk: infective endocarditis ($n = 12$), pneumonia ($n = 19$), abdominal sources ($n = 6$) and non-endocarditis vascular sources ($n = 2$).
[a]Only variables that remained and did not drop out of the final model are shown.
[b]Source of bacteraemia was grouped into one of three groups based on overall mortality risk (see text for details) and entered into the model as individual categories.

Renal Disease (MDRD) and the Cockcroft-Gault equations yielding different results (data not shown). This may be due to the fact that one (the Cockcroft-Gault equation) relies on body weight, whereas the other (the MDRD equation) does not; approximately 9% of patients weighed >100 kg in our study. Clinicians should therefore consider which formula to use in the context of their patient population. Notwithstanding these additional complexities, AUC estimation methods provide a more accurate assessment of vancomycin exposure than current dosing strategies dependant solely on vancomycin trough levels [28].

Clinicians should also be mindful of the impact of MIC results on the final AUC_{0-24}/MIC. This is attributed to the subtle differences between methodologies, with Etest generally yielding MIC results approximately one to two dilutions higher than BMD [29,30]. Similarly, inter-method differences exist with automated susceptibility platforms (e.g. Vitek2), yielding MIC results one to two dilutions lower than BMD [29,30]. These differences, although significant, can be easily circumvented by aiming for an appropriate MIC method-specific AUC_{0-24}/MIC target. This is not the case for automated susceptibility platforms, which require validation and establishment of a comparable AUC_{0-24}/MIC target before general implementation.

There are several limitations to our study, including the retrospective design. Our results require validation in patient groups excluded from our study, such as paediatric patients or patients receiving dialysis for chronic renal impairment. AUC estimation formulae as employed in our study assume linear vancomycin pharmacokinetics, stable renal clearance and volume of distribution and as such may not be applicable in morbidly obese or critically ill patients. As stored isolates were used for MIC determination, this may have affected the observed PK/PD targets. Other PK parameters, including protein binding or the free drug fraction, were not examined in this study [31].

In conclusion, vancomycin trough concentrations are unlikely to accurately reflect AUC_{0-24}/MIC targets and may result in suboptimal outcomes. AUC estimation based on validated formulae allow for individual patient dose optimization, resulting in increased treatment success when a vancomycin exposure or AUC_{0-24}/MIC_{BMD} of ≥398 is achieved. Furthermore, infection-specific targets may exist but require further study and confirmation before implementation.

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Transparency Declaration

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