The Emperor's New Clothes: Prospective Observational Evaluation of the Association between Initial Vancomycin Exposure and Failure Rates among Adult Hospitalized Patients with MRSA Bloodstream Infections (PROVIDE)

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Summary

A multicenter prospective study was performed to evaluate the relationship between day-2 vancomycin exposure profiles and outcomes in patients with MRSA bacteremia. The collective findings suggest that vancomycin dosing should be guided by the AUC and day-2 AUCs should be maintained between 400-515.

ABSTRACT

Background: Vancomycin is the most commonly administered antibiotic in hospitalized patients, but optimal exposure targets remain controversial. To clarify the therapeutic exposure range, this study evaluated the association between vancomycin exposure and outcomes in MRSA bacteremic patients.

Methods: Prospective, multicenter (n=14), observational study of 265 hospitalized adults with MRSA bacteremia treated with vancomycin. The primary outcome was treatment failure (TF), defined as 30-day mortality or persistent bacteremia ≥7 days. Secondary outcomes included acute kidney injury (AKI). The study was powered to compare TF between patients who achieved or did not achieve day-2 area under the curve to minimum inhibitory concentration (AUC/MIC) thresholds previously found to be associated with lower incidences of TF. The thresholds, analyzed separately as co-primary endpoints, were AUC/MIC by broth microdilution ≥650 and AUC/MIC by Etest ≥320.

Results: Treatment failure and AKI occurred in 18% and 26% of patients, respectively. Achievement of the pre-specified day-2 AUC/MIC thresholds was not associated with less TF. Alternative day-2 AUC/MIC thresholds associated with lower TF risks were not identified. A relationship between the day-2 AUC and AKI was observed. Patients with day-2 AUC ≤515 experienced the best global outcomes (no TF and no AKI).

Conclusions: Higher vancomycin exposures did not confer a lower TF risk but were associated with more AKI. The findings suggest that vancomycin dosing should be guided by the AUC and day-2 AUCs should be ≤515. As few patients had day-2 AUCs <400, further study is needed to define the lower bound of the therapeutic range.

Trial Registration: Registration was not required for this study.

Key words: vancomycin, MRSA, bacteremia, outcomes

INTRODUCTION

Vancomycin is the most commonly administered antibiotic in United States hospitals and a mainstay for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections for decades [1], yet optimal dosing of vancomycin is unclear [2]. For serious MRSA infections, current guidelines recommend targeting an area under the concentration time curve to minimum inhibitory concentration ratio (AUC/MIC) ≥400 [3]. As AUCs are not routinely determined in clinical practice, trough concentrations between 15-20 mg/L are used as a surrogate. Despite widespread clinical adoption of these recommendations [4], supportive data are limited and largely derived from single-center retrospective studies [5-11]. Furthermore, these critical vancomycin exposure targets were derived mostly with a simple and error-prone formula that approximated AUC values based upon the prescribed daily vancomycin dose and the patient's estimated renal function [6-9].

Bayesian software programs can generate accurate and reliable estimates of daily vancomycin AUCs with limited sampling [12,13]. Applying this method to estimate vancomycin exposures in a retrospective cohort of hospitalized, adult patients with MRSA bacteremia, Lodise and colleagues identified 2 AUC/MIC thresholds (AUC/MIC by broth microdilution [BMD] ≥650 and AUC/MIC by Etest™ ≥320) associated with a lower probability of treatment failure [14]. These thresholds were consistent with other recent studies that employed a similar Bayesian approach to estimate the vancomycin exposure profile [7,10]. However, prospective validation from larger-scale vancomycin exposure-response analyses that utilize individualized estimates of exposure based on measured concentrations has not been done. This multicenter,

observational study sought to evaluate prospectively the critical $AUC_{24\text{-}48}$/MIC exposure-outcome findings from the previous study by Lodise et al.

METHODS

Study design and population

This prospective, observational study was conducted in 14 centers between November 2014 and December 2015. The primary objective was to evaluate the impact of vancomycin AUC/MIC exposures on treatment failure rates among adult, hospitalized patients with MRSA bloodstream infections. The hypothesis was that patients who achieved day-2 AUC/MIC ratios above the thresholds (high exposure group) identified by Lodise and colleagues [14] will have 17.5% lower rates of failure relative to those with values below these thresholds (low exposure group). The thresholds, analyzed separately as co-primary endpoints, were AUC/MIC_{BMD} ≥650 and AUC/MIC_{Etest} ≥320. Day-2 vancomycin exposure was selected to best approximate near steady-state conditions of the initial vancomycin regimen. This also reflects contemporary clinical practice, in which vancomycin levels are frequently obtained on day 2.

Eligible participants were adult hospitalized patients with MRSA bacteremia who were treated with vancomycin within a window of 24 hours prior to and 48 hours after MRSA index blood culture collection, and whose vancomycin treatment continued for at least 72 hours after the index blood sample. Exclusion criteria were: absolute neutrophil count <500 cells/mL; renal replacement therapy for chronic renal failure during the first 5 days of vancomycin treatment; documented MRSA bacteremia within 60 days prior to the index blood sample; Acute

Physiology and Chronic Health Evaluation (APACHE) II score ≥26 [15]; and current participation in any antibiotic treatment intervention trial.

Evaluable patients were those who met inclusion and exclusion criteria; had a microbiology result from the central lab for the index MRSA blood culture; had at least 2 vancomycin blood concentrations during the first 5 days of vancomycin therapy (at least 1 sample had to be a non-trough vancomycin blood concentration collected on days 1-4 of vancomycin therapy); and had available outcome data 30 days after index blood culture collection. The study was conducted with a waiver of informed consent, consistent with CFR Title 45 part 46d, and the institutional review board at each site approved the study (see Supplementary Appendix: Patient Data for baseline patient data collected for the study).

Microbiologic data and phenotypic characterization

S. aureus was identified by standard methods. Oxacillin susceptibility was determined according to Clinical and Laboratory Standards Institute guidelines [16]. Isolates were stored in trypticase soy broth with 20% glycerol at -70°C. Isolates were shipped to JMI Laboratories (North Liberty, IA) for determination of BMD MIC, Etest™ MIC (according to the manufacturer's instructions - bioMérieux, Marcy l'Etoile, France), and heterogeneous vancomycin-intermediate *S. aureus* [17] (Supplementary Appendix: Microbiologic Methods).

Treatment data

All antibiotic treatment and vancomycin concentration data during the first 5 days of vancomycin treatment were collected. Vancomycin dosing and monitoring were at the

discretion of the treating clinician. As permitted by waiver of informed consent, vancomycin concentration could be assayed from leftover blood from standard-of-care blood draws. A trough sample was defined as one collected ≤2 hours prior to a vancomycin dose. A sample collected >2 hours prior to a vancomycin dose was considered non-trough. The vancomycin minimum concentration at hour 48 and AUC were estimated post-hoc using the maximal *a posteriori* probability procedure in ADAPT 5, which has been demonstrated as a way to estimate AUCs with low bias and high precision with limited pharmacokinetic (PK) sampling [12,13,18] (full details on PK modeling can be found in Supplemental Appendix: Pharmacokinetic Modeling). The day-2 AUC values were calculated post-hoc and were not used to guide the care of patients.

Outcomes

The primary outcome measure was treatment failure, defined as death within 30 days of index MRSA blood culture (30-day mortality) or growth of MRSA from a blood culture obtained ≥7 days after initiation of vancomycin therapy (i.e., persistent bacteremia) [14,19]. Secondary outcome measures included 30-day mortality; persistent bacteremia; and occurrence and time to onset of acute kidney injury (AKI) among patients with a baseline creatinine <2.0 mg/dL. The occurrence of AKI was assessed from initiation of vancomycin to 48 hours post-completion and was based on the definition of risk (post-baseline serum creatinine is ≥1.5*baseline serum creatinine) in the modified RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria [20] utilizing serum creatinine values and the vancomycin-induced nephrotoxicity (VINT)

definition in the vancomycin consensus guideline statement (defined as either a 50% or 0.5 mg/dL increase in serum creatinine, whichever was greater) [3].

Desirability of outcome ranking (DOOR) analysis was conducted post hoc [21,22]. Each patient was assigned an overall outcome based on the occurrences of 30-day mortality, persistent bacteremia, and AKI. The 5 outcome levels, from least to most desirable, were: (1) death; (2) survival with treatment failure and AKI; (3) survival with treatment failure and no AKI; (4) survival with treatment success and AKI; (5) survival with treatment success and no AKI. Partial credit weighting was used to explore whether varying the relative importance assigned to each outcome would affect the results (22) (see Supplementary Appendix: DOOR and Partial Credit Scoring).

Statistical methods

Based on the distribution of covariates among patients in a previous study [14], 250 evaluable patients were required for 80% power at a 2-sided alpha of 0.05 to detect a 17.5% difference in the primary treatment outcome variable between the pre-specified dichotomous AUC/MIC exposure variables assuming a 1-1.5 split in the distribution of the 250 evaluable patients in each exposure group. Assuming 80% of patients would be evaluable, approximately 312 patients were needed for this study. Inference was based on 2-sided 95% confidence intervals around treatment failure differences between high/low AUC/MIC exposure groups.

Secondary analyses consisted of estimating the differences between patients with high/low day-2 vancomycin exposures in proportions exhibiting the following outcomes: 30-day mortality, persistent bacteremia, and AKI. Kaplan-Meier plots were used to assess time to AKI.

Log-binomial regression was used to quantify associations between each AUC/MIC exposure variable and dichotomous outcome variables after adjusting for covariates. For the log-binomial analyses, the AUC/MIC exposure covariate was forced into the model first. For covariates associated with the outcome of interest having a likelihood ratio statistic p-value ≤0.10, the covariate with the lowest Akaike information criterion (AIC) was added to the model. Additional covariates were added to the model until the AIC no longer decreased. Exploratory relative risk (RR) threshold and classification and regression tree (CART) analyses were also performed to identify alternative optimal AUC/MIC ratios associated with failure and day-2 AUC threshold values associated with AKI (Supplemental Appendix: Relative Risk Threshold and Classification and Regression Tree Analyses).

DOOR analysis was conducted to examine the associations between the day-2 AUC, AUC/MIC by Etest™, and AUC and overall patient outcomes. Inverse probability of treatment weighting (IPTW) adjustments [23] were made for these prognostic factors: presence of endocarditis; baseline calculated creatinine clearance; APACHE II score; and presence of a prosthetic joint, cardiac prosthetic device, or intravascular prosthetic material. The ordinal outcomes included in the DOOR endpoint were also analyzed using a partial credit strategy (Supplemental Appendix: DOOR and Partial Credit Scoring). This approach is analogous to scoring an academic test, assigning 100% to the most desirable outcome, 0% to the least (e.g., death), and "partial credit" to each intermediate DOOR rank.

RESULTS

Patients

Of 310 patients enrolled across the 14 centers, 265 were evaluable (**Figure S1**). Five patients were enrolled in error, and 13 patients were found not to have met one or more entry criteria after enrollment (**Table S1**). Of the 292 enrolled patients who met entry criteria, 27 were deemed not evaluable due to 1 or more of the following: (1) unavailability of ≥1 required vancomycin concentrations (n=26), (2) missing index MRSA isolate (n=3), or (3) no 30-day outcome data (n=6) (**Table S2**).

The mean (standard deviation [SD]) age of evaluable patients was 61 (17) years, and mean APACHE II score was 12 (6); 29% of patients had possible or definite endocarditis. Eighty-six percent of isolates had an MIC by BMD of 0.5 or 1 mg/L, and 97% of isolates had an MIC by Etest™ of 1 or 1.5 mg/L (**Table 1**). Estimation of patient-specific exposures was based on 800 available concentrations among the 265 evaluable patients. A plot of the final PK dataset predicted vs observed vancomycin concentrations is shown in **Figure S2**. Altogether, 116 (44%) and 193 (73%) patients achieved an AUC/MIC_{BMD} ≥650 and AUC/MIC_{Etest} ≥320 (**Table 2**), respectively. Twenty-six patients (9.8%) had a decrease in vancomycin dose after day 2, while 21 patients (7.9%) had a dose increase; data on dosing frequency changes were not available. Baseline characteristics and distribution of microbiologic phenotypes between AUC/MIC exposure groups and treatment failure status are shown in **Table 2**.

Outcomes

Treatment failure did not differ by high vs low vancomycin exposure (AUC/MIC_{BMD} ≥650: 22% vs 15%, p=0.15; AUC/MIC_{Etest} ≥320: 21% vs 11%, p=0.07) (**Table 3**). No significant differences in proportions of patients exhibiting 30-day mortality or persistent bacteremia were noted between patients with drug exposures above vs below an AUC/MIC_{BMD} of 650 or AUC/MIC_{Etest} of 320 (**Table 3**). Results of the log-binomial analyses that adjusted for covariates associated with each outcome of interest at a p-value ≤0.1 were consistent with the bivariate comparisons (**Table 3**). The exploratory RR threshold and CART analyses did not locate alternative optimal critical AUC/MIC and AUC exposure thresholds associated with a lower risk of failure after multivariable adjustment for covariates associated with failure at a p-value ≤0.1 (**Figure S3 and Table 4**). As part of the exploratory analyses, an AUC/MIC_{BMD} of 400 was tested and was not found to be associated with treatment failure.

Acute kidney injury

In total, 212 patients had a baseline creatinine <2.0 mg/dL. The rates of AKI and VINT were higher in patients in the high AUC/MIC groups (**Table 3**), consistent with results of the Kaplan-Meier time-to-AKI analyses (**Figures S4 and S5**), which demonstrated differences in AKI and VINT between the binary AUC/MIC exposure groups. In the log-binomial regression, several confidence intervals around adjusted risk differences excluded the value zero for binary AUC/MIC exposure variables, indicating an increased risk of AKI and VINT with higher vancomycin exposure (**Table 3**). Exploratory RR threshold and CART analyses indicated that

patients with an AUC ≥793 relative to those with an AUC ≤343 were at greater risk for AKI and VINT (**Table 5**).

DOOR risk-benefit analysis

Of the 106 patients in the 2 lowest AUC exposure quintiles (AUC ≤515), 72% (95% CI, 68% to 76%) experienced the best global outcome, compared with the 3 higher exposure quintiles pooled (55% of 159 patients; 95% CI, 52% to 59%) (**Figure 1**). Results of the day-2 AUC/MIC_{BMD} and AUC/MIC_{Etest} DOOR analyses were consistent with the day-2 AUC DOOR analysis (**Figures S6 and S7**). Varying the partial credit weighting did not identify alternative exposure thresholds associated with more favorable global outcomes (**Figures S8 and S9**). Instead, under a range of partial credit scoring systems, outcomes still appeared better at lower AUC exposure thresholds.

DISCUSSION

In this prospective, multicenter study of adult patients with MRSA bacteremia, higher vancomycin exposures were not associated with a lower rate of failure but were associated with nephrotoxicity. The lack of benefit with higher vancomycin exposure is unlikely to be attributable to selecting the wrong thresholds, as exploratory analyses did not identify alternative optimal targets. Absence of benefit with higher vancomycin exposure additionally held true for analyses restricted to patients with an APACHE II score >10 and patients with infective endocarditis. Secondary efficacy outcome measures also did not differ between the pre-specified AUC/MIC exposure groups.

While efficacy was not associated with vancomycin exposure, the incidence of AKI was higher in patients with an AUC/MIC_{BMD} ≥650 and AUC/MIC_{Etest} ≥320. As is typical for non-immunologic drug-related AKIs, most events occurred after 5 days of therapy (**Figures S4 and S5**). The observed association between vancomycin exposure and nephrotoxicity is most plausibly driven by the AUC, as an antibacterial MIC has no pathophysiologic relationship to a patient's kidney function, and thus no causal association with AKI. Although this study lacked power to discriminate between dichotomous, ordinal, and continuous expressions of AUCs, an AUC-nephrotoxicity relationship clearly was present and existed in a stepwise fashion that persisted in the multivariable analyses, with incidence of AKI greatest among patients with an AUC ≥793 relative to those with an AUC ≤343 (**Table 5**). The AUC thresholds associated with increased risk of AKI in this study are notably consistent with previous reports [24-26].

The findings also suggest that vancomycin dosing should be guided by the AUC instead of the AUC/MIC ratio, and Bayesian software programs and simple analytic equations makes possible real-time, accurate measurement of the AUC with limited PK sampling [12,13]. The MIC value is of less importance for several reasons. First, there is a narrow range of vancomycin MIC values by BMD (the gold standard) among contemporary MRSA isolates (observed here and in other studies), with values of 0.5 or 1 mg/L in most institutions [27,28]. Second, there is inherent imprecision of MIC measurement, with a range of accuracy of ± 1 log2 dilutions [16,29], and a high degree of variability between MIC testing methods typically used in health care institutions [29,30]. Third, MIC values are typically not available within the first 72 hours of index culture collection, and thus cannot easily be incorporated into the initial dosing regimen.

Fourth, MIC has no causal relationship with AKI; vancomycin exposure is the physiologic driver of AKI.

For the day-2 AUC target range, we believe the collective study findings suggest that day-2 AUCs should be maintained below ~515 to maximize efficacy and minimize the likelihood of nephrotoxicity. This recommendation is supported by the results of the post-hoc DOOR analyses that demonstrated that patients in the lower 2 AUC quintiles (day-2 AUCs <515) had the best global outcomes (**Figure 1**). Additionally, the exploratory RR threshold and CART AUC-AKI analyses suggest that the risks of AKI and VINT were lowest among those with day-2 AUCs within this range (**Table 5**). Although global outcomes were similar between the 2 lower DOOR quintiles, we believe it is prudent to target an AUC of at least 400 since <20% of patients in this study had AUC values <400 and it is unclear whether efficacy outcomes are maintained at day-2 AUC values less than this threshold.

This study has several limitations. First are those inherent to an observational study design, including study selection bias due to the evaluability of patients, confounding, and non-standardized clinical management (including vancomycin dosing, monitoring, blood culture collection, and duration of therapy). However, baseline characteristics, comorbid conditions, measures of disease severity, and source control efforts were comparable between the high and low vancomycin exposure groups. This was a study of adult, non-neutropenic, non-dialysis patients, and the observed findings may not be applicable to other populations. Nearly all MRSA isolates had vancomycin MICs <2 mg/L. Although isolates with higher vancomycin MIC values are infrequently encountered in clinical practice, this is an important subset of MRSA bloodstream infections for which further study is needed. Our definition of treatment failure

was limited to objective measures to minimize any biases that may result from assessing and interpreting observational clinical data [19] but may not include all outcomes that are relevant to patients. Pharmacokinetic sampling was not completely standardized and included all PK samples collected over the first 5 days of therapy in an effort to gain the best individualized estimate of each patient's PK profile. As renal function varies over the initial course of therapy, we selected a population PK model as a Bayesian prior that made vancomycin clearance proportional to creatinine clearance. This permitted PK parameters to be estimated in the presence of changing renal function. Finally, the impact of dosing, dosing frequency, duration of therapy, and therapy switches were not considered, as the focus was to evaluate the association between the day-2 vancomycin exposure profile and outcomes. These covariates should be considered in future studies.

In conclusion, this study found no difference in treatment failure between the *a priori* specified vancomycin exposure groups among adults with MRSA bacteremia. While not associated with treatment failure, higher day-2 vancomycin exposures were associated with more nephrotoxicity. These results have important implications for clinical practice. Clinicians and guideline authors should reassess the balance of benefits and risks of targeting higher AUC/MIC for patients with MRSA bacteremia. In addition, the findings suggest that vancomycin dosing should be guided by the AUC instead of the AUC/MIC ratio and day-2 AUCs should be maintained below 515 to maximize efficacy and minimize the likelihood of AKI. It is unclear whether efficacy outcomes are maintained at day-2 AUC values <400 as few patients in this study had AUCs below this threshold. Further study is needed to define the lower bound of the day-2 AUC therapeutic range.

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Table 1. Baseline characteristics, distribution of microbiologic phenotypes, exposure variables, and outcomes

Demographics and baseline characteristics	**Values**
Male sex, n (%)	168 (63%)
Combined racial classes, n (%)	
Asian	4 (2%)
Black	70 (26%)
Other	6 (2%)
White	173 (65%)
Unknown	12 (5%)
Ethnicity, n (%)	
Not Hispanic or Latino	190 (72%)
Hispanic or Latino	12 (5%)
Unknown	63 (24%)
Age, years, mean (SD)	60.7 (17.3)
Weight, kg, mean (SD)	81.7 (24.9)
APACHE II score, mean (SD)	12 (6)
Bacterial complications, n (%)	
Presence of infective endocarditis-definite/possible	78 (29%)
Presence of internal prosthetic material	63 (24%)
Microbiologic phenotypes	
MIC_{BMD}*	
Range	0.25 to 2.0 mg/L*
$MIC_{50/90}$	1.0/1 mg/L
MIC_{Etest}**	
Range	0.5 to 2 mg/L**
$MIC_{50/90}$	1.5/1.5 mg/L
hVISA phenotype	0 (0%)

Demographics and baseline characteristics	Values
Day-2 vancomycin exposure variables, mean (SD)	
$Cmin_{48h}$	14.0 (6.2)
AUC	586.9 (235.5)
AUC/MIC_{BMD}	865.9 (425.2)
AUC/ MIC_{Etest}	475.7 (259.4)
Outcomes, n (%)	
Failure	**49 (18%)**
30-day mortality	30 (11%)
Persistent bacteremia	26 (10%)
60-day mortality	42 (16%)
Recurrence	9 (3%)
AKI***	55 (26%)
VINT***	60 (28%)

*Percentage of isolates with MIC_{BMD} of 0.5 and 1 mg/L: 25% and 72%.
**Percentage of Isolates with MIC_{Etest} of 1 and 1.5 mg/L: 29% and 57%.
***Among patients with baseline serum creatinine <2.0 mg/dL.

Abbreviations: AKI, acute kidney injury; AUC, area under the curve; Cmin, minimum blood plasma concentration; hVISA, heterogeneous vancomycin-intermediate *Staphylococcus aureus*; $MIC_{50/90}$, minimum inhibitory concentration that inhibits 50% and 90% of the isolates; MIC_{BMD}, minimum inhibitory concentration by broth microdilution; MIC_{Etest}, minimum inhibitory concentration by Etest; SD, standard deviation; VINT; vancomycin-induced nephrotoxicity.

Table 2. Comparison of baseline characteristics between patients with drug exposures above vs below: AUC/MIC_{BMD} of 650 and failure vs non-failure

Secondary Covariates	Failure Status			AUC/MIC_{BMD}			AUC/MIC_{Etest}		
	Failure (N=49)	Non-failure (N=216)	P-value	<650 (N=149)	≥650 (N=116)	P-value	<320 (N=72)	≥320 (N=193)	P-value
Male sex	30 (61%)	138 (64%)	0.73	91 (61%)	77 (66%)	0.37	41 (57%)	127 (66%)	0.18
Race									
Asian	0 (0%)	4 (2%)	0.55	3 (2%)	1 (1%)	0.08	1 (1%)	3 (2%)	0.95
Black	15 (31%)	55 (25%)		37 (25%)	33 (28%)		18 (25%)	52 (27%)	
Other	2 (4%)	4 (2%)		1 (1%)	5 (4%)		1 (1%)	5 (3%)	
White	31 (63%)	142 (66%)		98 (66%)	75 (65%)		48 (67%)	125 (65%)	
Unknown	1 (2%)	11 (5%)		10 (7%)	2 (2%)		4 (6%)	8 (4%)	
Weight, kg, mean (SD)	79.5 (21.5)	82.2 (25.6)	0.85	78.9 (23.9)	85.2 (25.7)	0.04	77.21 (22.69)	83.31 (25.47)	0.06
Body mass index, mean (SD)	28.1 (7.9)	27.6 (7.8)	0.57	26.9 (7.3)	28.8 (8.6)	0.11	26.86 (6.96)	28.04 (8.26)	0.38
Age, years, mean (SD)	68.8 (13.9)	58.8 (17.5)	<0.01	61.8 (17.5)	59.3 (17.0)	0.32	58.69 (17.94)	61.41 (17.02)	0.22
Residence in ICU at time of index blood culture collection	14 (29%)	45 (21%)	0.24	29 (19%)	30 (26%)	0.21	18 (25%)	41 (21%)	0.51
Type of MRSA									
Hospital/health care acquired	40 (82%)	147 (68%)	0.06	102 (68%)	85 (73%)	0.39	46 (64%)	141 (73%)	0.15
Community acquired	9 (18%)	69 (32%)		47 (32%)	31 (27%)		26 (36%)	52 (27%)	
Residence in health care institution for >72 hours in past 180 days	32 (65%)	115 (53%)	0.13	74 (50%)	73 (63%)	0.03	33 (46%)	114 (59%)	0.05

Secondary Covariates	Failure Status			AUC/MIC_{BMD}			AUC/MIC_{Etest}		
	Failure (N=49)	Non-failure (N=216)	P-value	<650 (N=149)	≥650 (N=116)	P-value	<320 (N=72)	≥320 (N=193)	P-value
Length of hospital stay (in days) prior to index culture, median (IQR)	0 (0, 0)	0 (0, 0)	0.76	0 (0, 0)	0 (0, 0)	0.45	0 (0, 0)	0 (0, 0)	0.35
APACHE-II score, mean (SD)	15.1 (5.5)	11.7 (5.4)	<0.01	11.9 (5.5)	12.8 (5.7)	0.25	11.36 (5.52)	12.67 (5.56)	0.10
Estimated creatinine clearance at baseline, mL/min, mean (SD)	60.4 (42.5)	91.1 (57.7)	<0.01	83.0 (49.9)	88.3 (63.8)	0.77	91.54 (52.64)	83.13 (57.69)	0.13
Diabetes mellitus	15 (31%)	75 (35%)	0.58	42 (28%)	48 (41%)	0.02	19 (26%)	71 (37%)	0.11
Heart failure (class II-IV)	13 (27%)	18 (8%)	<0.01	17 (11%)	14 (12%)	0.87	8 (11%)	23 (12%)	0.86
COPD	8 (16%)	36 (17%)	0.95	28 (19%)	16 (14%)	0.28	8 (11%)	36 (19%)	0.14
Transplanted organ	0 (0%)	14 (6%)	0.07	9 (6%)	5 (4%)	0.53	4 (6%)	10 (5%)	0.90
Active malignancy	7 (14%)	35 (16%)	0.74	26 (17%)	16 (14%)	0.42	10 (14%)	32 (17%)	0.59
Receipt of immunosuppressive drugs in last 30 days	5 (10%)	35 (16%)	0.29	29 (19%)	11 (9%)	0.02	11 (15%)	29 (15%)	0.96
Decubitus ulcers (stage II-IV)	8 (16%)	22 (10%)	0.22	16 (11%)	14 (12%)	0.73	6 (8%)	24 (12%)	0.35
Cerebrovascular accident	6 (12%)	21 (10%)	0.60	17 (11%)	10 (9%)	0.46	6 (8%)	21 (11%)	0.54
Surgery requiring >48 hours hospitalization in 30 days prior to date of index culture	4 (8%)	27 (13%)	0.39	14 (9%)	17 (15%)	0.19	6 (8%)	25 (13%)	0.30
Presence of infective endocarditis	22 (45%)	56 (26%)	<0.01	38 (26%)	40 (34%)	0.11	19 (26%)	59 (31%)	0.51
Pre-existing valvular heart disease	11 (22%)	18 (8%)	<0.01	17 (11%)	12 (10%)	0.78	6 (8%)	23 (12%)	0.41

Secondary Covariates	Failure Status			AUC/MIC$_{BMD}$			AUC/MIC$_{Etest}$		
	Failure (N=49)	Non-failure (N=216)	P-value	<650 (N=149)	≥650 (N=116)	P-value	<320 (N=72)	≥320 (N=193)	P-value
Previous infective endocarditis	2 (4%)	5 (2%)	0.49	3 (2%)	4 (3%)	0.47	3 (4%)	4 (2%)	0.34
Cardiac prosthetic device (e.g., pacemaker, cardioverter-defibrillator, prosthetic valve)	9 (18%)	14 (6%)	<0.01	9 (6%)	14 (12%)	0.08	7 (10%)	16 (8%)	0.71
Prosthetic joints	4 (8%)	16 (7%)	0.86	10 (7%)	10 (9%)	0.56	4 (6%)	16 (8%)	0.45
Intravascular prosthetic material (e.g., grafts, stents, etc.)	8 (16%)	24 (11%)	0.31	15 (10%)	17 (15%)	0.26	7 (10%)	25 (13%)	0.47
Receipt of antibiotic for at least 48 hours in the 30 days prior to index culture	15 (31%)	77 (36%)	0.50	56 (38%)	36 (31%)	0.27	23 (32%)	69 (36%)	0.56
Receipt of vancomycin ≥48 hours prior to index culture in 30 days prior to index culture	7 (14%)	18 (8%)	0.20	9 (6%)	16 (14%)	0.03	4 (6%)	21 (11%)	0.19
Polymicrobial bloodstream infection	1 (2%)	19 (9%)	0.11	11 (7%)	9 (8%)	0.91	4 (6%)	16 (8%)	0.45
Source of bacteremia infection - possibly to definitely									
Intravenous catheter	13 (27%)	58 (27%)	0.96	39 (26%)	32 (28%)	0.80	20 (28%)	51 (26%)	0.83
Urinary tract	7 (14%)	36 (17%)	0.68	23 (15%)	20 (17%)	0.69	11 (15%)	32 (17%)	0.80
Osteoarticular (bone and joint)	7 (14%)	39 (18%)	0.53	30 (20%)	16 (14%)	0.18	12 (17%)	34 (18%)	0.86
Skin and soft tissue	23 (47%)	95 (44%)	0.71	75 (50%)	43 (37%)	0.03	33 (46%)	85 (44%)	0.79

Secondary Covariates	Failure Status			AUC/MIC_{BMD}			AUC/MIC_{Etest}		
	Failure (N=49)	Non-failure (N=216)	P-value	<650 (N=149)	≥650 (N=116)	P-value	<320 (N=72)	≥320 (N=193)	P-value
Abdominal source	3 (6%)	17 (8%)	0.68	12 (8%)	8 (7%)	0.72	7 (10%)	13 (7%)	0.41
Central nervous system	2 (4%)	6 (3%)	0.63	4 (3%)	4 (3%)	0.72	1 (1%)	7 (4%)	0.34
Respiratory tract	7 (14%)	37 (17%)	0.63	24 (16%)	20 (17%)	0.81	8 (11%)	36 (19%)	0.14
Other	13 (27%)	30 (14%)	0.03	16 (11%)	27 (23%)	<0.01	11 (15%)	32 (17%)	0.80
Receipt of beta-lactam during first 7 days of vancomycin or >24 hours	25 (51%)	124 (57%)	0.42	79 (53%)	70 (60%)	0.23	39 (54%)	110 (57%)	0.68
Receipt of aminoglycoside during first 7 days of vancomycin or >24 hours[a]	4 (8%)	4 (2%)	0.02	4 (3%)	4 (3%)	0.72	2 (3%)	6 (3%)	0.89
Receipt of clindamycin during first 7 days of vancomycin or >24 hours	3 (6%)	6 (3%)	0.24	6 (4%)	3 (3%)	0.52	2 (3%)	7 (4%)	0.73
Receipt of fluoroquinolone during first 7 days of vancomycin or >24 hours	2 (4%)	13 (6%)	0.60	8 (5%)	7 (6%)	0.82	3 (4%)	12 (6%)	0.52
Receipt of rifampin during first 7 days of vancomycin or >24 hours[a]	4 (8%)	6 (3%)	0.07	5 (3%)	5 (4%)	0.69	0 (0%)	10 (5%)	0.05

Data presented as n (%), unless otherwise indicated.

[a]Fifteen patients received an aminoglycoside and/or rifampin. Among these patients, 5 were treatment failures; 3 of the 5 failures had an intravascular prosthetic device present.

Abbreviations: AUC, area under the curve; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range; MIC_{BMD}, minimum inhibitory concentration by broth microdilution; MIC_{Etest}, minimum inhibitory concentration by Etest; MRSA, methicillin-resistant *Staphylococcus aureus;* SD, standard deviation.

Table 3. Bivariate comparison of primary and secondary outcomes between patients with drug exposures above vs below: AUC/MIC_{BMD} of 650

Outcome	AUC/MIC_{BMD}	Proportion (%)	Risk Difference (95% CI)	
			Unadjusted	Adjusted
Treatment failure	≥650	15.44	0.07	0.03
	<650	22.41	(-0.03 , 0.17)	(-0.06 , 0.12)
Persistent bacteremia	≥650	8.05	0.04	0.01
	<650	12.07	(-0.03 , 0.11)	(-0.07 , 0.09)
30-day mortality	≥650	9.46	0.04	0.04
	<650	14.16	(-0.03 , 0.12)	(-0.02 , 0.10)
Acute kidney injury*	≥650	33.0	0.12	0.09
	<650	21.0	(0.00 , 0.24)	(-0.04 , 0.22)
Vancomycin-induced nephrotoxicity*	≥650	36.4	0.14	0.12
	<650	22.6	(0.01 , 0.26)	(-0.00 , 0.25)
Outcome	**AUC/MIC_{Etest}**	**Proportion (%)**	**Risk difference (95% CI)**	
			Unadjusted	**Adjusted**
Treatment failure	≥320	11.1	0.10	0.07
	<320	21.2	(0.01, 0.19)	(-0.07, 0.22)
Persistent bacteremia	≥320	5.56	0.06	0.07
	<320	11.4	(-0.01, 0.13)	(-0.05, 0.19)
30-day mortality	≥320	7.04	0.06	0.07
	<320	13.16	(-0.02, 0.14)	(-0.06, 0.20)
Acute kidney injury*	≥320	30.9	0.17	0.15
	<320	14.3	(0.05, 0.28)	(0.02, 0.29)
Vancomycin-induced nephrotoxicity*	≥320	33.6	0.18	0.16
	<320	15.9	(0.06, 0.29)	(0.02, 0.30)

*Patients with baseline serum creatinine (<2.0 mg/dL).

Abbreviations: AUC, area under the curve; CI, confidence interval; MIC_{BMD}, minimum inhibitory concentration by broth microdilution; MIC_{Etest}, minimum inhibitory concentration by Etest.

Table 4. Unadjusted and final model risk differences for failure by exploratory day-2 AUC & AUC/MIC predictors

Integrated exposure (PK & PD) measure	Exposure category	No. pts	Proportion (%)	Unadjusted		Adjusted	
				Point est.	95% CI	Point est.	95% CI
CART AUC/MIC_{BMD} cutpoint	≤345.88	30	3.33	0.17	(0.09, 0.25)	0.17	(-0.13, 0.48)
	>345.88	235	20.43				
RR AUC/MIC_{BMD} cutpoint	<500	85	11.76	0.10	(0.01, 0.19)	0.03	(-0.06, 0.11)
	≥500	180	21.67				
CART AUC/MIC_{Etest} cutpoint	<344.9	81	9.88	0.12	(0.04, 0.21)	0.10	(-0.04, 0.24)
	≥344.9	184	22.28				
RR AUC/MIC_{Etest} cutpoint	<350	83	10.84	0.11	(0.02, 0.20)	0.08	(-0.06, 0.22)
	≥350	182	21.98				

AUC, area under the curve; CART, classification and regression tree; CI, confidence interval; Est., estimate; MIC_{BMD}, minimum inhibitory concentration by broth microdilution; No., number; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; RR, relative risk.

Table 5. Acute kidney injury by exploratory day-2 AUC exposures

Categorical outcome	Integrated exposure (PK & PD) measure	Exposure category	No. pts	Proportion (%)	Cut-point level comparison	Unadjusted		Adjusted	
						Point est.	95% CI	Point est.	95% CI
AKI	CART AUC cutpoint	≤343	30	10	High vs low	0.29	0.08, 0.49	0.26	0.00, 0.51
		>343 to <793	151	26.49	High vs med	0.12	-0.06, 0.31	0.12	-0.07, 0.32
		≥793	31	38.71	Medium vs low	0.16	0.04, 0.29	0.14	-0.06, 0.33
	RR AUC cutpoint	<550	104	21.15		0.09	-0.02, 0.21	0.12	-0.01, 0.24
		≥550	108	30.56					
VINT	CART AUC cutpoint	≤343	30	10	High vs low	0.32	0.12, 0.52	0.27	0.01, 0.54
		>343 to <793	151	29.14	High vs med	0.13	-0.06, 0.32	0.13	-0.07, 0.32
		≥793	31	41.94	Medium vs low	0.19	0.06, 0.32	0.15	-0.06, 0.35
	RR AUC cutpoint	<550	104	23.08		0.10	-0.02, 0.22	0.12	0.00, 0.25
		≥550	108	33.33					

AKI, acute kidney injury; AUC, area under the curve; CART, classification and regression tree; CI, confidence interval; Est., estimate; No., number; PD, pharmacodynamic; PK, pharmacokinetic; pts, patients; RR, relative risk; VINT; vancomycin-induced nephrotoxicity.

Figure 1. Desirability of outcome ranking (DOOR) analysis by AUC quintiles