MAJOR ARTICLE

Impact of Vancomycin Exposure on Outcomes in Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia: Support for Consensus Guidelines Suggested Targets

Ravina Kullar,[1] Susan L. Davis,[1,3] Donald P. Levine,[2,3] and Michael J. Rybak[1,2,3]

[1]Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences, [2]Department of Medicine and Infectious Diseases, Division of Infectious Diseases, School of Medicine, [3]Wayne State University, Detroit Receiving Hospital and University Health Center, [4]Henry Ford Hospital, Detroit, Michigan

(See the article by Patel et al, on pages 969–974.)

Background. High rates of vancomycin failure in methicillin-resistant *Staphylococcus aureus* (MRSA) infections have been increasingly reported over time. The primary objective of our study was to determine the impact of vancomycin exposure and outcomes in patients with MRSA bacteremia initially treated with vancomycin.

Methods. This was a single-center retrospective analysis of 320 patients with documented MRSA bacteremia initially treated with vancomycin from January 2005 through April 2010. Two methods of susceptibility, Etest and broth microdilution, were performed for all isolates to determine the correlation of susceptibility testing to patient outcomes.

Results. Among a cohort of 320 patients, more than half (52.5%) experienced vancomycin failure. Independent predictors of vancomycin failure in logistic regression included infective endocarditis (adjusted odds ratio [AOR], 4.55; 95% confidence interval [CI], 2.26–9.15), nosocomial-acquired infection (AOR, 2.19; 95% CI, 1.21–3.97), initial vancomycin trough $<$15 mg/L (AOR, 2.00; 95% CI, 1.25–3.22), and vancomycin minimum inhibitory concentration (MIC) $>$1 mg/L by Etest (AOR, 1.52; 95% CI, 1.09–2.49). With use of Classification and Regression Tree (CART) analysis, patients with vancomycin area under the curve at 24 h (AUC_{24h}) to MIC ratios $<$421 were found to have significantly higher rates of failure, compared with patients with AUC_{24h} to MIC ratios $>$421 (61.2% vs 48.6%; $P = .038$)

Conclusions. In light of the high failure rates associated with this antimicrobial, optimizing the pharmacokinetic/pharmacodynamic properties of vancomycin by targeting higher trough values of 15–20 mg/L and AUC_{24h}/MIC ratios $\geq$400 in selected patients should be considered.

The frequency of infection due to methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasing for the past decade, with Rice et al identifying this organism as 1 of the 6 primary pathogens leading to resistance in the nosocomial setting [1, 2]. In fact, during 1999–2006, the percentage of *S. aureus* isolates from outpatient settings that were MRSA almost doubled, increasing by 10% every year [3]. Similarly, rates of MRSA infection identified in intensive care units (ICUs) have increased from 35.9% in 1992 to 64.4% in 2003, representing a 3.1% annual increase [4]. Unfortunately, MRSA infection has been associated with a longer hospital length of stay, higher hospital-associated costs, and increased morbidity and mortality, compared with methicillin-susceptible *S. aureus* (MSSA) infection [5, 6].

Vancomycin, a glycopeptide that was introduced over 50 years ago, has been the mainstay of treatment for invasive MRSA infection [7]. However, this antimicrobial is associated with several limitations, namely, its

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Correspondence: Michael J. Rybak, PharmD, MPH, Anti-Infective Research Laboratory, Dept of Pharmacy Practice, College of Pharmacy and Health Sciences, Wayne State University, 259 Mack Ave, Detroit, MI 48201 (m.rybak@wayne.edu).

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slow bactericidal activity, low penetration into certain tissues, increasing reports of resistance and failure, and potential minimum inhibitory concentration (MIC) "creep" [8, 9]. The vancomycin MIC has been used as a marker for therapeutic decision-making by clinicians and a predictor of failure, particularly in MRSA bacteremia and pneumonia. We recently reported findings on vancomycin susceptibility over 22 years in the Detroit metro area, revealing that, although the percentage of isolates for which the MIC was $\leq$0.5 μg/mL decreased over time, the percentage of isolates for which the MIC was $\geq$1 μg/mL increased from 80.7% to 93.4% during the same periods [10]. Similar findings of vancomycin MIC creep have been noted by various other investigators [11, 12]. However, there are conflicting data concerning whether this reported vancomycin MIC creep truly exists, with large surveillance reports failing to demonstrate significant changes in MICs [13, 14] and only reports from individual or regional institutions revealing this MIC creep. MRSA with higher MICs, in particular, MICs >1 mg/L, have been associated with vancomycin treatment failure [15, 16]. Vancomycin failure has also been associated with heteroresistant vancomycin-intermediate *S. aureus* (VISA), VISA, and vancomycin-resistant *S. aureus* (VRSA) strains; this association is of continued clinical concern [10, 17]. Moreover, several investigators have previously found prior vancomycin exposure, older age, and certain underlying disease states as independent predictors of vancomycin failure [16, 18]. On the basis of potentially improved penetration of vancomycin and clinical outcomes in patients with complicated infections, a consensus paper recently recommended that clinicians target higher serum trough concentrations of 15–20 mg/L to attain a vancomycin area under the curved in 24 h (AUC_{24h}) to MIC ratio $\geq$400 [19].

Currently, limited human and extrapolated data are available on the relevance of AUC_{24h}:MIC and vancomycin trough exposure in terms of outcomes for complicated bacteremia in patients. In an attempt to determine outcomes in patients treated with vancomcyin, our objective was to evaluate patients treated with vancomycin for MRSA bacteremia (MRSAB); characterize the risk factors for vancomycin failure, including vancomycin exposure; and describe the microbiological characteristics of patients with MRSAB.

METHODS

Study Population

This was a retrospective cohort study conducted at Detroit Medical Center (Detroit, MI). Adult patients who received vancomycin as initial therapy for at least 72 h for a documented MRSA bloodstream infection from January 2005 through April 2010 were included; only the first episode of bacteremia in each patient was included in the study population. Patients were excluded if they had received vancomycin therapy for <3 days. Data collected from patients' medical records included demographic characteristics, comorbidities, APACHE-II and Charlson score at the initiation of vancomycin therapy, source of MRSA bacteremia (eg, catheter or skin), antimicrobial treatment data, duration of bacteremia, response to vancomycin therapy, and microbiologic data. Vancomycin-induced nephrotoxicity was assessed, with nephrotoxicity was defined as a minimum of two or three consecutive documented increases in serum creatinine (defined as an increase of 0.5 mg/dl or $\geq$ 50% increase from baseline, whichever is greater) in the absence of an alternative explanation [19]. The initial vancomycin trough was evaluated for each patient at steady state (eg, immediately before the fourth dose) when available from clinical data, and $AUC_{0\text{-}24h}$ was estimated as the daily dose divided by clearance with use of standard population parameters for vancomycin clearance derived from a previous pharmacokinetic study performed at our institution [21].

Vancomycin treatment failure was defined as any of the following: (1) 30-day mortality; (2) persistent signs and symptoms of infection at the end of vancomycin therapy; or (3) persistent bacteremia defined as $\geq$7 days. Death was considered to be related to MRSAB if one of the following criteria were present: (1) blood cultures were positive for MRSAB at the time of death; (2) death occurred before the resolution of signs and symptoms of MRSAB; (3) death occurred at least 14 days after the onset of MRSAB without another explanation; (4) autopsy findings indicated MRSA infection as a cause of death; or (5) MRSAB was indicated as a cause of death on the death certificate. Length of hospital stay after infection was calculated from the first blood culture positive for *S. aureus* until discharge or death. Hospital-associated MRSAB was defined as a positive blood culture result $\geq$72 h after admission. The source of MRSAB was determined by the treating physician as documented in the patient's medical record.

Microbiological and Molecular Data

The first organism obtained from the patient's bloodstream was used for all microbiologic and molecular assessments. Stock solutions of vancomycin were prepared fresh before susceptibility testing and kept frozen at −4° C. Vancomycin analytical powder was obtained from Sigma Chemical Company. MICs were determined for each isolate in duplicate by nonautomated broth microdilution techniques with an inoculum of 5×10^5 colony-forming units/mL according to the Clinical and Laboratory Standards Institute guidelines [22]. Etest susceptibility was also performed on each isolate according to the manufacturer's instructions. Identification of heteroresistant VISA was determined using macro Etest methods and confirmed by modified population analysis

[10, 23], SCC*mec* type, USA strain type, the presence of the genes encoding Panton–Valentine leukocidin, and *agr* group and *agr* function were determined using previously described methods [24, 25].

Statistical Analysis

Categorical variables were compared using the χ^2 test, and continuous variables were compared by the Student's *t*-test or the Mann–Whitney *U* test. The CART technique was used to identify the significant breakpoint in the AUC_{24h}:MIC ratio.[26] A *P* value $<.05$ was considered to be statistically significant. To determine independent predictors of failure, backward stepwise logistic regression analysis was performed. Variables considered for model inclusion a priori were vancomycin MIC and those variables associated with failure in univariate analysis with a $P < 0.2$. All calculations were computed using PASW, version 18.0 (SPSS), and CART software (Salford Systems).

RESULTS

During the study period, 320 adult patients with MRSAB who received ⩾72 h of vancomycin therapy were included. A total of 168 patients (52.5%) experienced treatment failure with vancomycin according to the predefined definitions. With several patients falling into >1 category, breakdown of patients meeting failure criteria were as follows: 35 (21.0%) 30-day mortality, 93 (55.7%) persistent signs/symptoms of infection at the end of therapy, and 127 (76.0%) ⩾7 days of bacteremia. Of the 35 deaths, 26 (74.3%) were from MRSAB, with infective endocarditis and pneumonia being the most common concomitant sites of MRSA infection. Of the 9 patients for whom 30-day mortality was attributed to other causes, 8 had persistent signs and symptoms of infection at the end of therapy and/or ⩾ 7 days of bacteremia. A bivariate comparison of clinical and microbiologic characteristics between vancomycin treatment success and failures are displayed in Table 1, with both groups being similar in demographic characteristics. Concomitant sites of MRSA infection are displayed in Figure 1, with a higher percentage of patients with infective endocarditis failing vancomycin therapy than those without endocarditis (76.8% vs 46.7%; $P < 0.001$) and a lower percentage of patients with skin/wound infections failing therapy than those with other infection types (34.9% vs 56.0%; $P < .01$).

Three hundred eight (96%) of 320 patients had an initial vancomycin trough value available. Table 2 displays clinical failure rate according to initial vancomycin trough concentration. Concentrations of 15–20 mg/L were associated with significantly lower failure rates, compared with troughs of <10 mg/L or of 10–14.9 mg/L. Likewise, patients failing therapy had lower AUC_{24h}:MIC ratios and higher MIC values by Etest. The median (interquartile range [IQR]) of initial vancomycin troughs and AUC_{24h}:MIC ratios for success versus failure was 16.2 mg/L (12.0–19.9 mg/L) and 587.4 h (394.2–996.3 h) versus 13.5 mg/L (9.6–18.6 mg/L) and 537.3 h (330.7–959.8 h), respectively.

MIC distributions for vancomycin success versus failure by Etest and broth microdilution are displayed in Figures 2 and 3, respectively. The overall MIC distribution for Etest was 0.6% 0.38 mg/L, 8.8% 0.50 mg/L, 25.3% 0.75 mg/L, 27.2% 1 mg/L, 30.3% 1.5 mg/L, 7.5% 2 mg/L, and 0.3% 3 mg/L. The overall MIC distribution for broth microdilution was 19.4% 0.50 mg/L, 68.1% 1 mg/L, 12.2% 2 mg/L, and 0.3% 8 mg/L. Overall, molecular characteristics of the strains were as follows: 67.8% SCC*mec* IV and 32.2% SCC*mec* II, 52.2% PVL positive, 52.8% USA300, 57.8% *agr* I and 39.7% *agr* II, and 85% *agr* functional. There were no statistically significant differences in success versus failure detected as it related to

Table 1. Patient Characteristics

Characteristic	Vancomycin success median (IQR) or *n* (%) (*n*=152)	Vancomycin failure median (IQR) or *n* (%) (*n*=168)	*P* value
Age (years)	53 (45–64)	54 (46–61)	.75
APACHE-II score	7.5 (4–11)	8 (5–12)	.12
Weight (kg)	70.2 (64.0–82.0)	72.3 (63.0–86.9)	.29
Creatinine clearance (ml/min)	68.5 (35.8–98.6)	57.7 (25.0–92.8)	.18
Prior hospitalization <1 year	84 (55.3%)	79 (47.0%)	.14
Nosocomial-acquired infection	26 (17.1%)	41 (24.4%)	.11
Nursing home	25 (16.4%)	14 (8.3%)	.02
Diabetes	40 (26.3%)	41 (24.4%)	.67
Intravenous drug use	44 (28.9%)	63 (37.5%)	.11
Hemodialysis	18 (11.8%)	23 (13.7%)	.38
Vancomycin MIC >1 mg/L (Etest)	52 (34.2%)	66 (39.3%)	.35
Vancomycin MIC >1 mg/L (broth microdilution)	21 (13.8%)	20 (11.9%)	.42
Vancomycin monotherapy	126 (82.9%)	125 (74.4%)	.07

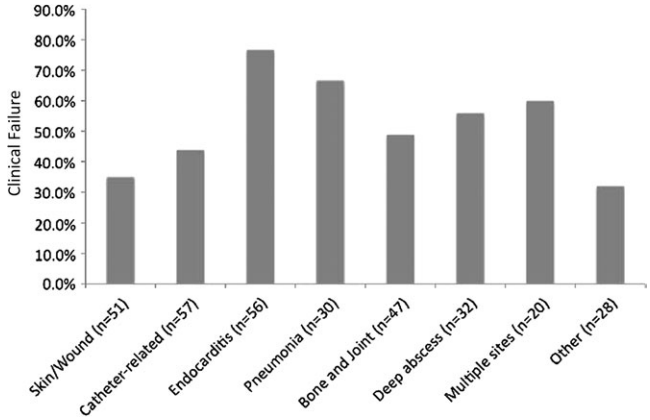

Figure 1. Vancomycin failure and concomitant sites of MRSA infection. Describes the proportion of patients that experienced clinical failure with vancomycin therapy according to concomitant sites of MRSA infection; the "other" group includes miscellaneous sites of infection, such as urinary tract infection, intra-abdominal infection, and necrotizing fasciitis, which could not be incorporated into a larger category.

these molecular findings. There were 18 heteroresistant VISA strains identified and verified in population analysis, and, although small in numbers, failure was significantly associated with heteroresistant VISA (failure 8.3% vs success 2.6%; $P = .024$).

Independent predictors of vancomycin failure in logistic regression included infective endocarditis (adjusted odds ratio [AOR], 4.55; 95% confidence interval [CI], 2.26–9.15; $P = .000$), nosocomial-acquired bacteremia (AOR, 2.19; 95% CI, 1.21–3.97; $P = .009$), initial vancomycin trough <15 mg/L (AOR, 2.00; 95% CI, 1.25–3.22; $P = .004$), and vancomycin MIC >1 mg/L by Etest (AOR, 1.52; 95% CI, 1.09–2.49; $P = .045$). Using CART analysis, we found that patients with vancomycin AUC_{24h}:MIC ratios <421 had a significantly higher rate of failure, compared with patients with AUC_{24h}:MIC ratios ≥ 421 (61.2% vs 48.6%; $P = .038$).

The median (IQR) hospital length of stay for patients succeeding versus failing vancomycin treatment was 11 days (8–17 days) versus 18 days (12–30 days), respectively, with $P < .001$. Nephrotoxicity during vancomycin therapy was significantly higher in patients who experienced failure (20.2% vs 10.5%; $P = .044$). However, a greater percentage of patients in the vancomycin failure group who experienced nephrotoxicity were receiving concomitant aminoglycosides (19.6% vs 11.2%). The percentage of nephrotoxicity for each vancomycin trough range is shown in Table 2. Compared with vancomycin troughs of 15–20 mg/L, patients with initial troughs >20 mg/L were significantly more likely to experience nephrotoxicity during therapy. Furthermore, patients who developed nephrotoxicity while receiving vancomycin had a significantly longer length of hospital stay (20 vs 13 days; $P = .001$).

DISCUSSION

This is one of the largest cohorts evaluating outcomes and characteristics of patients with MRSAB treated initially with vancomycin for ≥ 72 h. More than half (52.5%) of the patients with MRSAB experienced failure of vancomycin therapy, with 76% of these patients experiencing ≥ 7 days of bacteremia. Among the group of patients with initial vancomycin trough concentrations of 15–20 mg/L, the rate of failure was statistically lower; however, a nearly 40% failure rate was observed even among these patients. Infective endocarditis, nosocomial-acquired bacteremia, initial vancomycin trough <15 mg/L, and vancomycin MIC >1 mg/L (Etest) were found to be associated with failure. There have been varying definitions of vancomycin failure used in the literature, with common criteria of failure being persistence of bacteremia, which has ranged from 3 days to the end of therapy [27, 28]. We used ≥ 7 days of bacteremia as part of our composite definition, because this has been the most widely used definition of persistence of bacteremia. Although many patients treated with vancomycin for bacteremia or endocarditis are ultimately cured without a change to another antibiotic, that other antibiotics routinely achieve faster resolution is consistent with the poor relative performance of the drug and is an important factor in evaluating patient response for an infection that is associated with high morbidity and mortality.

There are limited and conflicting data correlating vancomycin trough concentrations with clinical efficacy [29–32]. In light of the 2009 vancomycin consensus guidelines recommending targeting trough levels of 15–20 mg/L in patients with complicated

Table 2. Vancomycin Trough Concentrations and Poor Outcomes

Characteristic $N = 308$[a]	Vancomycin failure *n* (%)	*P* (vs reference category)	Nephrotoxicity[b] *n* (%)	*P* (vs reference category)
Trough <10 mg/L (*n*=70)	46 (65.7%)	0.001	10/65 (15.4%)	.682
Trough 10–14.9 mg/L(*n*=90)	52 (57.8%)	0.016	13/76 (17.1%)	.476
Trough 15–20 mg/L(n=86)	34 (39.5%)	REF	10/77 (13.0%)	REF
Trough >20 mg/L(n=62)	31 (50.0%)	0.206	17/62 (27.4%)	.032

[a] Twelve patients without trough concentrations drawn at steady state were excluded from analysis.

[b] Denominators reflect exclusion of patients with end-stage renal disease from analysis of nephrotoxicity.

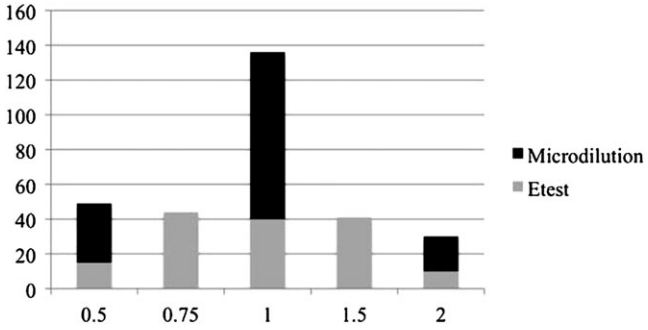

Figure 2. MIC distributions for patients with Vancomycin success via Etest and broth microdilution ($n = 152$).

MRSA infections, of note, we found that a higher percentage of patients failed vancomycin therapy that did not achieve this initial trough target, highlighting the possible correlation of vancomycin exposure and patient outcomes. In addition, a higher percentage of patients with serious invasive infection, such as endocarditis and pneumonia, in which high serum bactericidal activity may be preferred, failed vancomycin therapy. Other studies may have failed to correlate higher vancomycin troughs with clinical outcome because of small sample size and/or small number of patients with deep-seeded infection. Of interest, CART analysis identified patients with vancomycin AUC_{24h}:MIC ratios <421 as more likely to fail vancomycin therapy, which is similar to what has been recommended for successful therapy in the recent consensus guidelines; however, these higher ratios may contribute to greater nephrotoxicity [19, 20]. However, this specific AUC:MIC ratio should be interpreted with some caution, because achieving this target is highly dependent on the MIC distribution and there are multiple approaches for determining AUC. Although we used a demographic population-based model from our own institution, the true interpatient variation of drug exposure may be more precisely evaluated using a MAP-Bayesian approach [33, 34].

A majority of our MRSA strains were SCC*mec* IV, PVL positive, and *agr* I, suggesting community origin [35]. This may

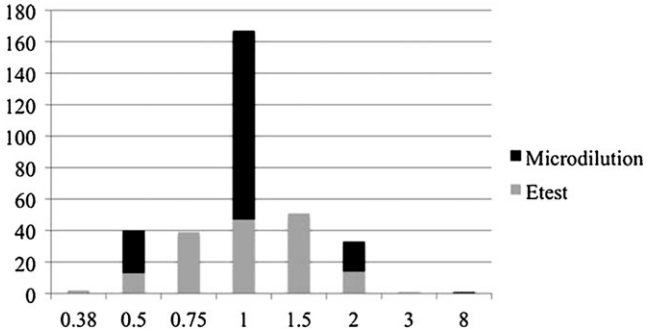

Figure 3. MIC distributions for patients with Vancomycin failure via Etest and broth microdilution ($n = 168$).

partially explain why a majority of the isolates exhibited vancomycin MICs ≤ 1 mg/L, because SCC*mec* IV has been associated with lower MICs than more traditional SCC*mec* II or nosocomial-associated MRSA infection [36, 37]. Furthermore, 85% of our strains were *agr* functional. Fowler et al [38] demonstrated that *agr* dysfunction was associated with persistent bacteremia and vancomycin failure. We were unable to demonstrate an association between *agr* dysfunction and patient outcome. This may be becauase of the higher rates of SCC*mec* IV strains and, therefore, the lower percentage of patients with dysfunctional agr loci. We previously reported these differences on *agr* function and SCC*mec* type from our medical center [39]. Vancomycin MICs differed depending on the susceptibility method used, with a higher percentage of patients having isolates with vancomycin MICs >1 mg/L by the Etest method. Sader et al [40] reported similar findings; susceptibility testing was performed by both Etest and broth microdilution in 1800 MRSA bloodstream isolates. The authors found that Etest provided vancomycin MIC results that were consistently 0.5–1.5 $\log_2$ dilution steps higher than those provided by the microdilution method. Hsu et al [41] found a wide discordance among the 4 susceptibility test methods (Etest, microdilution, Vitek-1, and Microscan) frequently used in clinical laboratories, with the least variability found between Etest and Microscan results. Of interest, several investigators have previously correlated high vancomycin MICs with treatment failure [9, 15, 16]. Of importance, all of these studies correlating high vancomycin MICs to treatment failure used the Etest as their susceptibility testing method. In this investigation, we performed MIC susceptibility testing with use of both Etest and broth microdilution and found an association with vancomycin MIC >1 mg/L by Etest but no correlation with patients' outcomes and MIC testing by broth microdilution. In a post hoc sensitivity analysis, multiple comparisons of vancomycin MICs were evaluated against patient outcome, and consistently stronger associations were seen with Etest than with broth microdilution. This may in part be attributable to the ability to determine more strata in the MIC distribution with Etest, allowing for measurements in between traditional dilution steps. Recently, Vaudaux et al [42] found discrepancies among broth microdilution, macrodilution, and Etest for detecting glycopeptide-intermediate isolates of *S. aureus* for vancomycin and teicoplanin. The authors hypothesized that the 20-fold lower inoculum size that is used for broth microdilution may explain, in part, the tendency to observe lower MICs to vancomycin and teicoplanin, compared with other methods. Further research to determine the impact of these findings on clinical decision-making and patient outcome is warranted.

In conclusion, although vancomycin has been the mainstay of treatment for invasive MRSA infection, our results indicated a high failure rate of $>50\%$ among patients with MRSAB treated

initially with vancomycin. Although the improvement observed could be considered modest, our research suggests that targeting initial higher trough levels of 15–20 mg/L may improve outcomes in select patients with complicated bacteremia.

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