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 ⩾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

Received 11 October 2010; accepted 27 January 2011.

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).

Clinical Infectious Diseases 2011;52(8):975–981

1058-4838/2011/528-0002$14.00
DOI: 10.1093/cid/cir124

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 ≤0.5 μg/mL decreased over time, the percentage of isolates for which the MIC was ≥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 ≥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 ≥ 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 ≥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 ≥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

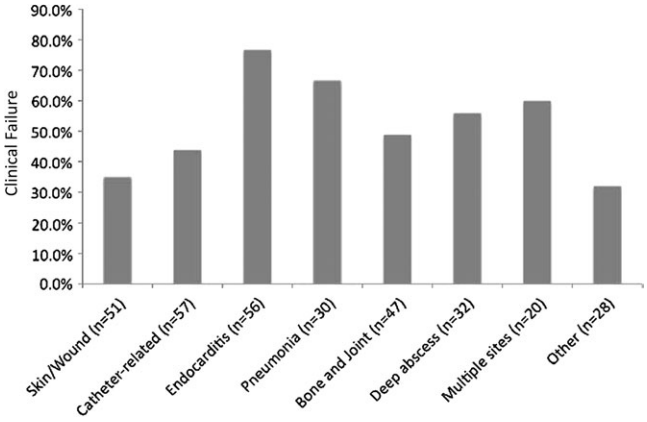

Figure 1. Vancomycin failure and concomitant sites of MRSA infection. Describes the proportion of patients that experienced clinical failure with vancomycin therapy according to concomitant sites of MRSA infection; the "other" group includes miscellaneous sites of infection, such as urinary tract infection, 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.

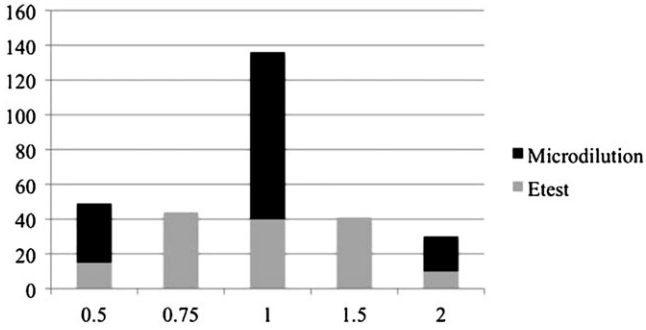

Figure 2. MIC distributions for patients with Vancomycin success via Etest and broth microdilution ($n = 152$).

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

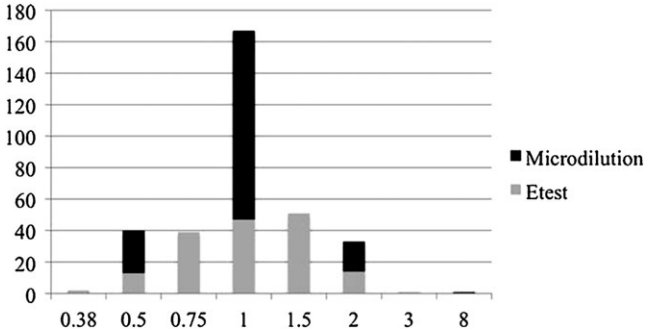

Figure 3. MIC distributions for patients with Vancomycin failure via Etest and broth microdilution ($n = 168$).

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.

Acknowledgments

Potential conflicts of interest. S. L. D. has received research support from Ortho-McNeil; has served as a consultant to Pfizer, Cubist, and Ortho-McNeil; and has served on speaker's bureau for Pfizer. D. P. L. has received research support from Cubist, Theravance, Nabi, Astellas, 3M, and Johnson & Johnson; has served as a consultant to Cubist and Pfizer; and has served on speaker's bureaus for Cubist and Pfizer. M. J. R. has received research grants from Astellas, Cubist, Forest, and Pfizer; has served as a consultant to Astellas, Cubist, Forest, and Ortho-McNeil; and has served on speaker's bureaus for Cubist, Novartis, and Pfizer. R. K. certifies no potential conflicts of interest.

References

1. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control **2004**; 32:470–85.
2. Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis **2008**; 197:1079–81.
3. Klein E, Smith DL, Laxminarayan R. Community-associated methicillin-resistant *Staphylococcus aureus* in outpatients, United States, 1999–2006. Emerg Infect Dis **2009**; 15:1925–30.
4. Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R. Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992–2003. Clin Infect Dis **2006**; 42:389–91.
5. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol **2005**; 26:166–74.
6. Lodise TP, McKinnon PS. Clinical and economic impact of methicillin resistance in patients with *Staphylococcus aureus* bacteremia. Diagn Microbiol Infect Dis **2005**; 52:113–22.
7. Levine DP. Vancomycin: a history. Clin Infect Dis **2006**; 42(Suppl 1); S5–12.
8. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis **2006**; 42(Suppl. 1);S35–9.
9. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. J Clin Microbiol **2004**; 42:2398–402.
10. Rybak MJ, Leonard SN, Rossi KL, Cheung CM, Sader HS, Jones RN. Characterization of vancomycin-heteroresistant *Staphylococcus aureus* from the metropolitan area of Detroit, Michigan, over a 22-year period (1986 to 2007). J Clin Microbiol **2008**; 46:2950–4.
11. Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001–05. J Antimicrob Chemother **2007**; 60:788–94.
12. Wang G, Hindler JF, Ward KW, Bruckner DA. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. J Clin Microbiol **2006**; 44:3883–6.
13. Jones RN. Microbiological features of vancomycin in the 21st century: minimum inhibitory concentration creep, bactericidal/static activity, and applied breakpoints to predict clinical outcomes or detect resistant strains. Clin Infect Dis **2006**; 42(Suppl 1);S13–24.
14. Sader HS, Fey PD, Limaye AP, et al. Evaluation of vancomycin and daptomycin potency trends (MIC creep) against methicillin-resistant *Staphylococcus aureus* isolates collected in nine U.S. medical centers from 2002 to 2006. Antimicrob Agents Chemother **2009**; 53:4127–32.
15. Lodise TP, Graves J, Evans A, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant *Staphylococcus aureus* bacteremia treated with vancomycin. Antimicrob Agents Chemother **2008**; 52:3315–20.
16. Soriano A, Marco F, Martinez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis **2008**; 46:193–200.
17. Maor Y, Hagin M, Belausov N, Keller N, Ben-David D, Rahav G. Clinical features of heteroresistant vancomycin-intermediate *Staphylococcus aureus* bacteremia versus those of methicillin-resistant S. aureus bacteremia. J Infect Dis **2009**; 199:619–24.
18. Khatib R, Johnson LB, Fakih MG, et al. Persistence in *Staphylococcus aureus* bacteremia: incidence, characteristics of patients and outcome. Scand J Infect Dis **2006**; 38:7–14.
19. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Pharmacotherapy **2009**; 29:1275–9.
20. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother **2008**; 52:1330–6.
21. Ducharme MP, Slaughter RL, Edwards DJ. Vancomycin pharmacokinetics in a patient population: effect of age, gender, and body weight. Ther Drug Monit **1994**; 16:513–8.
22. Clinical and Laboratory Institute. Methods for dilution antimicrobial susceptibility test for bacteria that grow aerobically; approved standard. 8th ed. Wayne, PA: CLISI, 2009.
23. Wootton M, MacGowan AP, Walsh TR, Howe RA. A multicenter study evaluating the current strategies for isolating *Staphylococcus aureus* strains with reduced susceptibility to glycopeptides. J Clin Microbiol **2007**; 45:329–32.
24. Zhang K, McClure JA, Elsayed S, Louie T, Conly JM. Novel multiplex PCR assay for characterization and concomitant subtyping of staphylococcal cassette chromosome mec types I to V in methicillin-resistant *Staphylococcus aureus*. J Clin Microbiol **2005**; 43: 5026–33.
25. Lina G, Piemont Y, Godail-Gamot F, et al. Involvement of Panton-Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. Clin Infect Dis **1999**; 29:1128–32.
26. Zhang H, Singer B. Recursive partitioning in the health sciences. New York: Springer, 1999.
27. Khatib R, Saeed S, Sharma M, Riederer K, Fakih MG, Johnson LB. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of *Staphylococcus aureus* bacteremia. Eur J Clin Microbiol Infect Dis **2006**; 25:181–5.
28. Howden BP, Johnson PD, Ward PB, Stinear TP, Davies JK. Isolates with low-level vancomycin resistance associated with persistent methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2006**; 50:3039–47.
29. MacGowan AP. Pharmacodynamics, pharmacokinetics, and therapeutic drug monitoring of glycopeptides. Ther Drug Monit **1998**; 20:473–7.
30. Moellering RC Jr. Monitoring serum vancomycin levels: climbing the mountain because it is there? Clin Infect Dis **1994**; 18:544–6.
31. Jeffres MN, Isakow W, Doherty JA, et al. Predictors of mortality for methicillin-resistant *Staphylococcus aureus*health-care-associated pneumonia: specific evaluation of vancomycin pharmacokinetic indices. Chest **2006**; 130:947–55.
32. Hermsen ED, Hanson M, Sankaranarayanan J, Stoner JA, Florescu MC, Rupp ME. Clinical outcomes and nephrotoxicity associated with

vancomycin trough concentrations during treatment of deep-seated infections. Expert Opin Drug Saf **2010**; 9:9–14.
33. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis **2009**; 49:507–14.
34. Bhavnani SM, Rubino CM, Ambrose PG, Drusano GL. Daptomycin exposure and the probability of elevations in the creatine phosphokinase level: data from a randomized trial of patients with bacteremia and endocarditis. Clin Infect Dis **2010**; 50:1568–74.
35. Hiramatsu K, Cui L, Kuroda M, Ito T. The emergence and evolution of methicillin-resistant *Staphylococcus aureus*. Trends Microbiol **2001**; 9:486–93.
36. Musta AC, Riederer K, Shemes S, et al. Vancomycin MIC plus heteroresistance and outcome of methicillin-resistant *Staphylococcus aureus* bacteremia: trends over 11 years. J Clin Microbiol **2009**; 47:1640–4.
37. Sakoulas G, Eliopoulos GM, Fowler VG Jr, et al. Reduced susceptibility of *Staphylococcus aureus* to vancomycin and platelet microbicidal protein correlates with defective autolysis and loss of accessory gene regulator (agr) function. Antimicrob Agents Chemother **2005**; 49:2687–92.
38. Fowler VG Jr, Sakoulas G, McIntyre LM, et al. Persistent bacteremia due to methicillin-resistant *Staphylococcus aureus* infection is associated with agr dysfunction and low-level in vitro resistance to thrombin-induced platelet microbicidal protein. J Infect Dis **2004**; 190:1140–9.
39. Tsuji BT, Rybak MJ, Cheung CM, Amjad M, Kaatz GW. Community- and health care-associated methicillin-resistant *Staphylococcus aureus:* a comparison of molecular epidemiology and antimicrobial activities of various agents. Diagn Microbiol Infect Dis **2007**; 58:41–7.
40. Sader HS, Rhomberg PR, Jones RN. Nine-hospital study comparing broth microdilution and Etest method results for vancomycin and daptomycin against methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **2009**; 53:3162–5.
41. Hsu DI, Hidayat LK, Quist R, et al. Comparison of method-specific vancomycin minimum inhibitory concentration values and their predictability for treatment outcome of meticillin-resistant *Staphylococcus aureus* (MRSA) infections. Int J Antimicrob Agents **2008**; 32:378–85.
42. Vaudaux P, Huggler E, Bernard L, Ferry T, Renzoni A, Lew DP. Underestimation of vancomycin and teicoplanin MICs by broth microdilution leads to underdetection of glycopeptide-intermediate isolates of *Staphylococcus aureus*. Antimicrob Agents Chemother Sep **2010**; 54:3861–70.

Vancomycin: We Can't Get There From Here

Nimish Patel,[1] Manjunath P. Pai,[1] Keith A. Rodvold,[5] Ben Lomaestro,[3,4] George L. Drusano,[2] and Thomas P. Lodise[1,2]

[1]Albany College of Pharmacy and Health Sciences, [2]Ordway Research Institute, [3]Albany Medical Center Hospital; [4]Albany Medical College, Albany, New York; and [5]University of Illinois at Chicago, Chicago, Illinois

(See the article by Kullar et al, on pages 975–981.)

Background. We sought to characterize the pharmacodynamic profile of the more intensive vancomycin dosing regimens currently used in response to the recent vancomycin guidelines.

Methods. A series of Monte Carlo simulations was performed for vancomycin regimens ranging from .5 g intravenous (IV) Q12H to 2 g IV Q12H. The probability of achieving an AUC/MIC ratio ⩾ 400 for each dosing regimen was calculated for minimum inhibitory concentrations (MICs) from .5 to 2 mg/L. The risk of nephrotoxicity for each regimen was derived from a previously published vancomycin trough-nephrotoxicity logistic regression function. Restricted analyses were performed that only included subjects with troughs between 15 and 20 mg/L.

Results. At a MIC of 2 mg/L, even the most aggressive dosing regimen considered (2 g every 12 h) only yielded a probability of target attainment (PTA) of 57% while generating a nephrotoxicity probability upward of 35%. At a MIC of 1 mg/L, ⩾3 g per day provided PTA in excess of 80% but were associated with unacceptable risks of nephrotoxicity. In the restricted analyses of subjects with troughs between 15 and 20 mg/L, all regimens produced a PTA of 100% at MICs ⩽1 mg/L. The PTA was variable among the regimens at a MIC of 2 mg/L and was highly dependent on the total daily dose administered.

Conclusions. This study indicates that vancomycin may not be useful for treating serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections with MIC values > 1 mg/L where PTA is questionable. Since an AUC/MIC ratio ⩾ 400 is target associated with efficacy, one should consider incorporating computation of AUC when monitoring vancomycin.

Despite the widespread use of vancomycin in response to increases in the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) both in hospital and the community, there has been an inadequate examination of its exposure-response profile against MRSA [1, 2]. The recent vancomycin therapeutic monitoring guidelines recommend more aggressive vancomycin dosing schemes, maintaining vancomycin troughs between 15 and 20 mg/L "based on the potential to increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections caused by *S. aureus*" [3]. However, studies characterizing the pharmacodynamic profile of the more intensive vancomycin dosing regimens used in response to the guidelines have not been performed.

When evaluating the exposure-response profile of an antibiotic, there are several things to consider. First, therapy should have a high likelihood of achieving the exposure target associated with maximal response among the pathogens likely to be encountered in clinical practice. While a variety of pharmacodynamic indices have been suggested for vancomycin, data suggest that a near maximal bactericidal effect is achieved against MRSA when the ratio of the vancomycin area under the concentration-time curve and the minimum inhibitory concentrations (AUC/MIC) exceeds 400 [4–7].

Examination of effect alone is not sufficient when describing the exposure-response profile of an antibiotic. It is also critical to assess the probability of toxicity associated with the regimens used in practice. While the association between vancomycin and neprotoxicity has

Received 26 September 2010; accepted 18 January 2011.

Correspondence: Thomas P. Lodise, PharmD, Associate Professor, Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, 106 New Scotland Avenue, Albany, NY 12208 (thomas.lodise@acphs.edu).

Clinical Infectious Diseases 2011;52(8):969–974

1058-4838/2011/528-0001$14.00
DOI: 10.1093/cid/cir078

been the subject of considerable debate, recent data suggests that vancomycin exposure-nephrotoxicity response relationship exists and the initial vancomycin trough is the pharmacodynamic index that best describes this association [8–13].

Finally, it is important to recognize that to truly understand the relationship between drug exposure and the response, these relationships must be viewed in an integrated fashion. This investigation sought to characterize exposure-response profiles of the more intensive empiric vancomycin dosing regimens currently used in practice in response to the recent vancomycin guidelines. Monte Carlo simulation was used to quantify the probability of target attainment (PTA) profile and the risk of nephrotoxicity for vancomycin dosing schemes of varying intensity over the range of MRSA MIC values deemed susceptible by CLSI [14]. Since vancomycin is renally excreted from the body and exposure changes as a function of creatinine clearance (CL_{CR}), we evaluated these exposure-response relationships across different renal function strata. We also examined the pharmacodynamic profile of maintaining troughs between 15–20 mg/L and 10–15 mg/L.

METHODS

Vancomycin Population Pharmacokinetic Model

Vancomycin exposure profiles were estimated from a previously published open 2-compartment population pharmacokinetic (PK) model of 37 patients with varying degrees of renal function who received vancomycin therapy for a presumed or documented Gram-positive infection [15–17]. In this model, vancomycin clearance (CL_V) was made proportional to creatinine clearance (CL_{CR}) plus an intercept term (non–renal clearance estimate). The mean (standard deviation) values of the PK parameter estimates were: volume of distribution (Vd) = 18.25 (8.88) L, $CL_{intercept}$ = .48 (.30) L/h, CL_{slope} = .83 (.67) L/h, intercompartmental rate constant from the central compartment to the peripheral compartment (K_{cp}) = 2.36 (4.22) h^{-1}, and intercompartmental rate constant from the peripheral compartment to the central compartment (K_{pc}) = 2.27 (7.08) h^{-1}.

Monte Carlo Simulation

A series of 9999 subject Monte Carlo simulations (MCS) were performed for vancomycin dosing regimens using total daily doses ranging from 1 to 4 g in 1 g increments, divided every 12 h (500 mg intravenous [IV] Q12H, 1000 mg IV Q12H, 1500 mg IV Q12H, and 2000 mg IV Q12H) [18]. For each simulated regimen, the estimated CL_{CR} was fixed at values of 1.2, 2.4, 3.6, 4.8, 6.0, and 7.2 L/h. Parameter values from the lognormal distributions were used to simulate plasma concentration-time curves for dosing regimens. Plasma concentration-time profiles were not adjusted for protein binding.

The $AUC_{72\text{-}96h}$ was determined for each regimen at the 6 prespecified CL_{CR} values. The $AUC_{72\text{-}96h}$ was calculated by integrating the plasma concentration-time profile from time zero (start of administration) to 72 and 96 h after start of administration and taking the difference between $AUC_{0\text{-}72h}$ and $AUC_{0\text{-}96h}$. For each regimen simulated, the fraction of subjects achieving an $AUC_{72\text{-}96h}$/MIC ratio $\geq$400 within each CL_{CR} stratum was calculated for MIC values from .5 mg/L to 2 mg/L. The $AUC_{72\text{-}96h}$ was used as the AUC exposure endpoint for efficacy because it closely approximates 24-h steady state AUC values (AUC exposure evaluated in previous analyses) and aligns with the $Cmin_{96h}$ endpoint for toxicity (see below).

To assess probability of toxicity, vancomycin trough concentrations at hour 96 ($Cmin_{96h}$) were simulated for each regimen at the 6 prespecified CL_{CR} values. The initial vancomycin trough nephrotoxicity logistic regression function from our previous publication was used to assess the median (interquartile range) probability of nephrotoxicity for each of the simulated vancomycin dosing regimens within each CL_{CR} stratum [8]. The likelihood of nephrotoxicity was estimated separately for intensive care unit (ICU) and non-ICU patients. Since our initial model was derived from a population with initial trough <30 mg/L, we did not estimate the probability of nephrotoxicity for CL_{CR} strata with estimated median trough in excess of 30 mg/L [8].

INTEGRATED PROBABILITY OF TARGET ATTAINMENT AND NEPHROTOXICITY ANALYSIS

To estimate overall probability of achieving an AUC/MIC ratio $\geq$400 and risk of nephrotoxicity for each vancomycin regimen, a 9999 subject Monte Carlo simulation was performed for each of the 4 vancomycin dosing regimens using the mean (standard deviation) CL_{CR} value from a 415-subject nosocomial pneumonia (NP) clinical trial as the estimate of CL_{CR} variability [19]. The mean (standard deviation) for this population was 5.3 (2.58) L/h. The $AUC_{72\text{-}96h}$ and $Cmin_{96h}$ was estimated for each regimen, and the fraction of subjects achieving an AUC/MIC ratio $\geq$400 for MIC values of .5 mg/L to 2 mg/L was calculated. The risk of a nephrotoxic event among ICU and non-ICU patients for each regimen was determined as described above. Restricted analyses were also performed that only included subjects among the 4 simulated vancomycin regimens that achieved $Cmin_{96h}$ values between 15–20 and 10–15 mg/L. In these restricted analyses, the fraction of subjects achieving an AUC/MIC ratio $\geq$400 for MIC values of .5 to 2 mg/L was calculated for each regimen.

RESULTS

The median (IQR) $AUC_{72\text{-}96h}$ and $Cmin_{96h}$ values, stratified by CL_{CR}, for the vancomycin dosing regimens from the MCS analysis are displayed in Table 1. As one would expect, there was

Table 1. Median (Interquartile Range) $AUC_{0\text{-}24h}$ and $Cmin_{96h}$ Values From the Monte Carlo Simulation Analysis for Four Vancomycin Dosing Regimens, Stratified by CL_{CR}

CLCR	1.2 L/h	2.4 L/h	3.6 L/h	4.8 L/h	6.0 L/h	7.2 L/h
500 mg IV every 12 h						
AUC72-96h	607 (414–846)	396 (265–563)	296 (199–429)	237 (158–346)	197 (132–292)	169 (112–251)
Cmin96h	18.5 (11.6–27.3)	10.6 (5.9–16.7)	6.9 (3.5–11.7)	4.9 (2.1–8.7)	3.6 (1.3–6.8)	2.7 (.9–5.5)
1000 mg IV every 12 h						
AUC72-96h	1214 (827–1693)	792 (530–1127)	593 (398–857)	474 (315–692)	395 (262–581)	338 (224–503)
Cmin96h	37.0 (23.1–54.6)	21.2 (11.9–33.3)	13.9 (6.9–23.4)	9.7 (4.2–17.5)	7.2 (2.7–13.7)	5.5 (1.7–11.1)
1500 mg IV every 12 h						
AUC72-96h	1822 (1241–2539)	1188 (795–1690)	889 (596–1286)	710 (473–1039)	591 (396–875)	508 (337–754)
Cmin96h	55.7 (34.7–82.0)	31.7 (17.8–50.5)	20.7 (10.3–34.9)	14.6 (6.4–26.5)	10.8 (4.1–20.5)	8.2 (2.6–16.7)
2000 mg IV every 12 h						
AUC72-96h	2429 (1655–3385)	1588 (1076–2276)	1182 (793–1712)	947 (631–1385)	789 (528–1166)	677 (452–1010)
Cmin96	74.3 (46.3–109.3)	42.3 (23.8–67.3)	27.7 (13.7–46.5)	19.4 (8.5–35.3)	14.3 (5.4–27.4)	10.9 (3.4–22.2)

an inverse relationship between $AUC_{72\text{-}96h}$ and CL_{CR}, and $Cmin_{96h}$ and CL_{CR} among all dosing strategies evaluated. The relationship between $AUC_{72\text{-}96h}$ and $Cmin_{96h}$ varied across the different dosing regimens and CL_{CR}. The $Cmin_{96h}$ value associated with an $AUC_{72\text{-}96h}$ given value was highly dependent on the dose administered and CL_{CR}. Analogously, discordant $AUC_{72\text{-}96h}$ values were observed for dosing regimens with similar $Cmin_{96h}$ values.

The probability of achieving an AUC/MIC ratio ⩾400, stratified by MIC value and CL_{CR}, is displayed in Table 2. At a MIC value of .5 mg/L, the PTA exceeded 80% across CL_{CR} values when the total daily vancomycin dose was ⩾2 g. At a MIC value of 1 mg/L, the probability of achieving an AUC/MIC ⩾ 400 was variable. The PTA was <80% for most CL_{CR} strata with 500 mg IV Q12H or 1000 mg IV Q12H. In contrast, the PTA exceeded 80% with 1500 mg IV Q12H or 2000 mg IV Q12H for most CL_{CR} strata. At a MIC of 2 mg/L, the probability of achieving an AUC/MIC ⩾ 400 was <80% for all regimens except 2 g IV Q12H at CL_{CR} values of 1.2 and 2.4 L/h.

The probability of a nephrotoxic event for each vancomycin dosing regimen, stratified by ICU status and CL_{CR}, is displayed in Table 3. Across all CL_{CR} strata, there was a dose-response relationship between ascending daily doses of vancomycin administered and the risk of nephrotoxicity and likelihoods were highest among ICU subjects. At all doses evaluated, the probability of a nephrotoxic event and CL_{CR} were inversely related.

Using the distribution of CL_{CR} from a NP clinical trial [19], the overall probability of achieving an AUC/MIC ratio ⩾400 and risk of nephrotoxicity for each vancomycin dosing regimen is displayed in Table 4. Both the overall PTA and probability of a nephrotoxic event increased as the intensity of the vancomycin daily dose increased. The probability of a nephrotoxic event also increased as a function of dosing frequency and ICU status. Similar to the stratified CL_{CR} PTA analyses, PTA was suboptimal at an MIC value of 2 mg/L. At a MIC of 1 mg/L, ⩾3 total g per day provided PTA in excess of ~80%, but these dosing schemes were associated with considerable risks of nephrotoxicity, especially for subjects in the ICU.

The results of the restricted analysis that assessed probability of achieving an AUC/MIC ratio ⩾400 for MIC values of .5 to 2 mg/L among subjects with $Cmin_{96h}$ values between 15–20 and 10–15 mg/L for each simulated regimen are displayed in Figures 1 and 2, respectively. When $Cmin_{96h}$ values were restricted to 15–20 mg/L, the observed PTA was 100% at MIC values of .5 and 1 mg/L for all regimens. In contrast, the PTA was variable among the regimens at a 2 mg/L and was highly dependent on the daily dose administered. A more favorable PTA at a 2 mg/L was observed with higher daily doses relative to lower daily doses yielding the same trough range (15–20 mg/L). When the analysis

Table 2. Probability of Achieving an AUC/MIC Ratio of 400 for Each Vancomycin Regimen Stratified by Renal Function

CLCR	1.2 L/h	2.4 L/h	3.6 L/h	4.8 L/h	6.0 L/h	7.2 L/h
500 mg IV every 12 h						
0.5 mg/L	94%	87%	75%	61%	49%	39%
1.0 mg/L	77%	49%	29%	17%	10%	6%
2.0 mg/L	29%	8%	2%	1%	0.3%	0.2%
1000 mg IV every 12 h						
0.5 mg/L	98%	97%	95%	92%	86%	80%
1.0 mg/L	94%	87%	75%	61%	49%	39%
2.0 mg/L	77%	49%	29%	17%	10%	6%
1500 mg IV every 12 h						
0.5 mg/L	99%	98%	98%	97%	96%	93%
1.0 mg/L	97%	95%	90%	82%	74%	66%
2.0 mg/L	89%	75%	57%	42%	30%	22%
2000 mg IV every 12 h						
0.5 mg/L	99%	99%	99%	99%	98%	97%
1.0 mg/L	98%	97%	95%	92%	87%	81%
2.0 mg/L	94%	87%	75%	61%	49%	39%

Table 3. Median (Inter-quartile Range) Probability of a Neprotoxic Event for Each Vancomycin Regimen Stratified by Renal Function

	Residence in non-ICU				Residence in ICU			
CLCR	0.5 g Q12H	1 g Q12H	1.5 g Q12H	2 g Q12H	0.5 g Q12H	1 g Q12H	1.5 g Q12H	2 g Q12H
1.2 L/h	15 (7–34)	NA	NA	NA	37 (21–63)	NA	NA	NA
2.4 L/h	7 (4–13)	20 (8 – NA)	NA	NA	19 (12–32)	45 (21 – NA)	NA	NA
3.6 L/h	4 (3–8)	10 (4–25)	19 (6 – NA)	35 (9 – NA)	13 (9–21)	26 (13–52)	44 (18 – NA)	64 (25 – NA)
4.8 L/h	3 (3–5)	6 (3–14)	10 (4–32)	17 (5 – NA)	11 (8–16)	17 (10–35)	27 (12–61)	40 (15 – NA)
6.0 L/h	3 (2–4)	5 (3–9)	7 (3–19)	10 (4–35)	9 (7–13)	13 (8–25)	19 (10–43)	27 (11–63)
7.2 L/h	3 (2–4)	4 (2–7)	5 (3–13)	7 (3–22)	8 (7–11)	11 (7–20)	15 (8–32)	19 (9–48)

NOTE. NA: not applicable. The initial logistic regression model only included a limited number of patients with troughs >30 mg/L

was restricted to patients with $Cmin_{96h}$ values between 10 and 15 mg/L, the observed PTA was 100% at a MIC value of .5 mg/L and variable at 1 and 2 mg/L. Similar to the 15–20 mg/L PTA analysis, PTA varied as a function of daily dose.

DISCUSSION

Overall, we found that the more intensive vancomycin dosing regimens empirically used in practice in response to the recent vancomycin guidelines were not consistently capable of effectively achieving an acceptable PTA at higher MIC values nor were they able to keep toxicity to a minimum. When one takes an expectation over the CL_{CR} values likely to be encountered in clinical practice (for this we used the distribution of CL_{CR} from a NP clinical trial), even the most aggressive dosing regimen (4 g IV daily) considered only yielded a PTA of 57% at an MIC value of 2 mg/L while increasing the risk of nephrotoxicity upward of 35%. Total daily doses <4 g daily have even lower PTA, albeit with slightly lower toxicity burdens and cannot be recommended for therapy when MIC values equal 2.0 mg/L. More intensive dosing regimens cannot be considered because the risk of toxicity is too great.

For MRSA infections with a MIC value of 1 mg/L, the PTA values were improved relative to those seen at an MIC of 2 mg/L. Despite this improvement in PTA, the PTA was highly variable across CL_{CR} strata when daily doses of ≤2 g were used. Vancomycin regimens consisting of at least 3 g daily were necessary to achieve PTA values ~80% at a MIC value of 1 mg/L. However, dosing regimens containing at least 3 g daily were associated with an elevated risk of nephrotoxicity, especially among subjects with lower CL_{CR} values and for those residing in the ICU. It was only at a MIC value of .5 mg/L when both PTA and nephrotoxicity risks were highly acceptable at doses >1 g per day. This may be the only scenario where vancomycin can be effectively used without an excessive probability of a nephrotoxic event.

Another noteworthy finding in our analysis was the high degree of variability between $AUC_{72\text{-}96h}$ and $Cmin_{96h}$ values. The recent vancomycin guidelines recommend monitoring trough concentrations as a surrogate for AUC values. This recommendation is troubling because we observed a wide range of AUC values from several different dosing regimens yielding isometric Cmin values and vice versa. The $AUC_{72\text{-}96h}$ associated with a given trough value was highly dependent on the daily dose administered and the CL_{CR}.

The therapeutic discordance between $AUC_{72\text{-}96h}$ and $Cmin_{96h}$ values is further highlighted by the restricted PTA analyses, which only considered subjects with Cmin of 15–20 mg/L for each simulated regimen (Figure 1). Although PTA was highly acceptable for MIC values ≤1 mg/L for all regimens, PTA at 2 mg/L was variable and highly dependent on the daily dose administered.

Table 4. Overall Probability of Achieving an AUC/MIC Ratio of 400, by MIC Value, Versus the Probability of a Nephrotoxic Event

	AUC/MIC ratio ≥400			Nephrotoxic event	
MIC value	0.5mg/L (%)	1.0mg/L (%)	2.0mg/L (%)	Non-ICU (%)	ICU (%)
500 mg IV Q12H	57	15	0.7	3	10
1000 mg IV Q12H	90	57	15	6	16
1500 mg IV Q12H	97	79	38	9	25
2000 mg IV Q12H	98	90	57	14	34

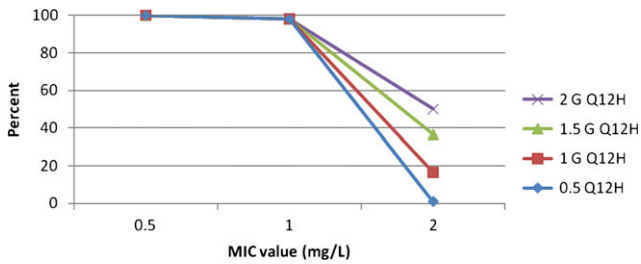

Figure 1. Probability of achieving AUC/MIC ratio ≥ 400 for vancomycin regimens of varying intensity when Cmin values were between 15 and 20 mg/L. Among the 9999 subjects simulated, the total number of subjects with Cmin values 15–20 mg/L were (*A*) 406 subjects (0.5G Q12h), (*B*) 1100 subjects (1G Q12h), (*C*) 1190 subjects (1.5G Q12h), and (*D*) 1096 subjects (2G Q12h).

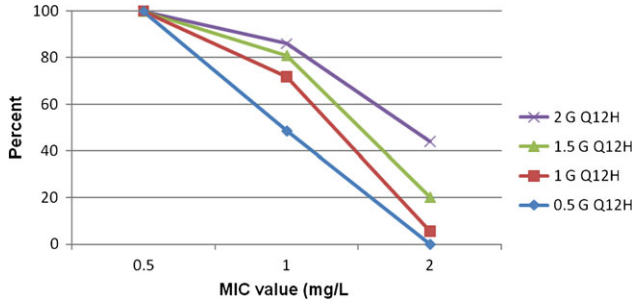

Figure 2. Probability of achieving AUC/MIC ratio ⩾400 for vancomycin regimens of varying intensity when Cmin values were between 10 and 15 mg/L. Among the 9999 subjects simulated, the total number of subjects with Cmin values 10–15 mg/L were (*A*) 1091 subjects (0.5G Q12h), (*B*) 1690 subjects (1G Q12h), (*C*) 1508 subjects (1.5G Q12h), and (*D*) 1177 subjects (2G Q12h).

This finding is not surprising because the AUC is the integrated quantity of drug exposure (the serum drug concentration time curve) over a defined interval and reflects the cumulative exposure over time. In contrast, the Cmin represents a single exposure point at the end of the dosing interval. It is unreasonable to expect a single exposure point at the end of the dosing interval to be representative of the entire concentration-time interval. It is also important to note that, while PTA was variable, the risk of nephrotoxicity was the same for all regimens producing Cmin values of 15–20 mg/L, regardless of total daily dose, since nephrotoxicity is more closely linked to the Cmin than the AUC.

While Cmin appears to be a good marker of likelihood of toxicity, these data call into question the practice of monitoring trough values for effect. Our data demonstrated that Cmin values between 15 and 20 mg/L do not consistently result in AUC/MIC ratios ⩾400 when the MIC is 2 mg/L. Conversely, regimens producing troughs of 15–20 mg/L are not always needed to achieve an AUC/MIC ratios ⩾400 when the MIC is 1 mg/L. Since an AUC/MIC ratio ⩾400 is considered to be the most important pharmacodynamic parameter associated with positive clinical outcome, one should consider incorporating computation of AUC when monitoring vancomycin therapy rather than solely using Cmin as a surrogate for both effect and toxicity. We support the use of Cmin monitoring for assessment of a subject's probability of experiencing a nephrotoxic event while on vancomycin therapy but believe AUC calculations are warranted if AUC/MIC ratio ⩾400 is truly the pharmacodynamic target of interest, especially when the MIC value is 2 mg/L. Calculation of AUC can be accomplished by dividing the daily dose by clearance, where clearance is estimated by CL_{CR}. Alternatively, CL_V can be more accurately calculated in a patient by taking 2 or 3) timed sample measurements (ie, Cmax and Cmin). Although, determination of the vancomycin Cmax has been promoted as unnecessary, measurement of this value can improve estimation of AUC to optimize effect.

Our findings also question the need for trough values of 15–20 mg/L for all patients. Our results indicate that regimens producing trough values in excess of 15 mg/L are not always necessary to provide an AUC/MIC ratio ⩾400, especially if the MIC is ⩽1 mg/L (Figure 2). By minimizing the trough needed to achieve the desired AUC value, we may be able to reduce the risk of nephrotoxicity associated with vancomycin.

Several things should be noted when interpreting these results. First, the pharmacodynamic target for vancomycin (AUC/MIC ratio ⩾400) against MRSA is based on limited clinical data. The best data available are from a retrospective evaluation of patients with *S. aureus* in a community hospital over a 1 year period [4]. There were only a small number of MRSA isolates in the database, and a number of the patients had combination agent chemotherapy. Nonetheless, a number of different analyses identified AUC/MIC ratios of 350–400 (total drug) as being related to clinical outcome for patients with Staphylococcal nosocomial pneumonia, and this is consistent with in vitro and animal model studies [4–6,20–24]. Although these are the best available data to date, it highlights the major importance in identifying a better estimate of the pharmacodynamic target for good clinical response than that currently available.

Second, the pharmacodynamic target for vancomycin (AUC/MIC ratio ⩾400) was based on broth microdilution (BMD) MIC testing [4]. Similar to most mathematical expressions, the denominator drives this relationship. The higher the MIC value, the lower the measure of drug exposure relative to the MIC and the lower the level of the expected microbiological effect. This is important to note because of the increased use of Etest to quantify MIC values and data showing Etest yield higher MIC values relative to BMD for a given MRSA strain [25]. For now, our results should be viewed in relation to BMD results and clinical studies are needed to define the AUC/MIC ratio needed for maximal effect using the Etest as the measure of potency.

Third, there is little information available with regard to the protein binding of vancomycin. Previous reports have differed considerably with respect to the amount of free drug [26]. It is therefore a high priority to identify the range of protein binding observed clinically for this agent so that the free drug AUC/MIC ratio target can be properly estimated and the true therapeutic window for vancomycin be elucidated for seriously ill patients. Fourth, our results only apply to serious infections due to MRSA. Our results should not be generalized for less severe infection types and other pathogens.

Overall, this study demonstrated that the utility of vancomycin be questioned for MRSA isolates with an MIC >1.0 mg/L where PTA is questionable. Total daily doses of vancomycin ⩽4 g were not able to achieve an acceptable PTA for infections with an MIC value of 2 mg/L. For infections with an MIC value of 1 mg/L, only aggressive doses of vancomycin were able to achieve a satisfactory PTA but with a high risk of nephrotoxicity,

especially for patients residing in the ICU. Given the prevalence of patients with MRSA infections with MIC values >1 mg/L, our results indicate that vancomycin cannot safely achieve the desired PD target. In these patients, alternative anti-MRSA agents should be considered. Before other agents can be definitively recommended over vancomycin, data are sorely needed to determine whether alternative antibiotic can remedy the outcomes observed with vancomycin for MRSA infections with high vancomycin MIC values >1 mg/L. In addition, further studies are needed to determine if optimization of vancomycin therapy can improve outcomes without subjecting patients to an increased risk of vancomycin-related toxicities.

Acknowledgments

Potential conflicts of interest. N. P., B. M. L., and K. A. R. report having no conflicts of interest. M. P. P. has received grant support from Pfizer Inc and Roche. G. L. D. has received consulting income and grant support from Forest Laboratories. T. P. L. is a consultant for Pfizer, Cubist Pharmaceuticals, Astellas, and Forest. T. P. L. is a speaker for Pfizer, Cubist Pharmaceuticals, and Astellas. T. P. L. has received grant support from Astellas, Cubist, and Pfizer.

References

1. Lodise TP Jr., McKinnon PS. Burden of methicillin-resistant *Staphylococcus aureus*: focus on clinical and economic outcomes. Pharmacotherapy **2007**; 27:1001–12.
2. Kirst HA, Thompson DG, Nicas TI. Historical yearly usage of vancomycin. Antimicrob Agents Chemother **1998**; 42:1303–4.
3. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm **2009**; 66:82–98.
4. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. Clin Pharmacokinet **2004**; 43:925–42.
5. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am **2003**; 17:479–501.
6. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis **2006**; 42(Suppl 1):S35–9.
7. Drusano GL. Antimicrobial pharmacodynamics: critical interactions of 'bug and drug'. Nat Rev Microbiol **2004**; 2:289–300.
8. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis **2009**; 49:507–14.
9. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med **2006**; 166:2138–44.
10. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. Clin Ther **2007**; 29:1107–15.
11. Ingram PR, Lye DC, Fisher DA, Goh WP, Tam VH. Nephrotoxicity of continuous versus intermittent infusion of vancomycin in outpatient parenteral antimicrobial therapy. Int J Antimicrob Agents **2009**; 34:570–4.
12. Ingram PR, Lye DC, Tambyah PA, Goh WP, Tam VH, Fisher DA. Risk factors for nephrotoxicity associated with continuous vancomycin infusion in outpatient parenteral antibiotic therapy. J Antimicrob Chemother **2008**; 62:168–71.
13. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrob Agents Chemother **2008**; 52:1330–6.
14. (CLSI). CaLSI. M2-M9-Performance standards for antimicrobial disk susceptibility tests; approved standards-ninth edition.
15. Rodvold KA, Blum RA, Fischer JH, et al. Vancomycin pharmacokinetics in patients with various degrees of renal function. Antimicrob Agents Chemother **1988**; 32:848–52.
16. Drusano GL, Ambrose PG, Bhavnani SM, et al. Vancomycin dose recommendations for hospital-, ventilator- or health care-associated pneumonia and the attainment of vancomycin trough concnetrations of 15–20 mg/L dissonance. In: 45th Annual Meeting of the Infectious Diseases Society of America. San Diego, CA: 2007.
17. Rodvold KA, Pryka RD, Garrison M, Rotschafer JC. Evaluation of a two-compartment Bayesian forecasting program for predicting vancomycin concentrations. Ther Drug Monit **1989**; 11:269–75.
18. D'Argenio DZ, Schumitzky A. ADAPT II. A program for simulation, identification, and optimal experimental design. Los Angeles, California: User manual, Biomedical Simulations Resource, University of Southern California, 1997.
19. West M, Boulanger BR, Fogarty C, et al. Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. Clin Ther **2003**; 25:485–506.
20. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clin Infect Dis **1998**; 26:1–10; quiz 1–2.
21. Rybak MJ. Pharmacodynamics: relation to antimicrobial resistance. Am J Med **2006**; 119(6 Suppl 1);S37–44: discussion; S62–70.
22. Harigaya Y, Bulitta JB, Forrest A, et al. Pharmacodynamics of vancomycin at simulated epithelial lining fluid concentrations against methicillin-resistant *Staphylococcus aureus* (MRSA): implications for dosing in MRSA pneumonia. Antimicrob Agents Chemother **2009**; 53:3894–901.
23. LaPlante KL, Leonard SN, Andes DR, Craig WA, Rybak MJ. Activities of clindamycin, daptomycin, doxycycline, linezolid, trimethoprim-sulfamethoxazole, and vancomycin against community-associated methicillin-resistant *Staphylococcus aureus* with inducible clindamycin resistance in murine thigh infection and in vitro pharmacodynamic models. Antimicrob Agents Chemother **2008**; 52:2156–62.
24. Lubenko IY, Strukova EV, Smirnova MV, et al. Telavancin and vancomycin pharmacodynamics with *Staphylococcus aureus* in an in vitro dynamic model. J Antimicrob Chemother **2008**; 62:1065–9.
25. Prakash V, Lewis JS 2nd, Jorgensen JH. Vancomycin MICs for methicillin-resistant *Staphylococcus aureus* isolates differ based upon the susceptibility test method used. Antimicrob Agents Chemother **2008**; 52:4528.
26. Berthoin K, Ampe E, Tulkens PM, Carryn S. Correlation between free and total vancomycin serum concentrations in patients treated for Gram-positive infections. Int J Antimicrob Agents **2009**; 34:555–60.