

Serum Vancomycin Levels Resulting From Continuous or Intermittent Infusion in Critically Ill Burn Patients With or Without Continuous Renal Replacement Therapy

Kevin S. Akers, MD,*† Jason M. Cota, PharmD,‡ Kevin K. Chung, MD,†§
Evan M. Renz, MD,†§ Katrin Mende, PhD,*|| Clinton K. Murray, MD*†

We evaluated vancomycin levels as recent guidelines for therapeutic monitoring of vancomycin (not available at the time these data were collected) recommend trough levels of 15 to 20 $\mu\text{g}/\text{mL}$; however, this may be more difficult to achieve in patients with accelerated vancomycin clearance, such as burn patients or recipients of continuous venovenous hemofiltration (CVVH) therapy. We retrospectively studied 2110 serum vancomycin levels of 171 patients admitted to the burn intensive care unit for more than 4 years and who received vancomycin by continuous infusion (CI) or intermittent infusion (II), with or without simultaneous CVVH. In-hospital mortality, 14- and 28-day mortality following vancomycin therapy were not different between dosing methods, although increased mortality was observed in the subgroup of patients receiving CI vancomycin empirically for clinical sepsis with negative blood cultures. More vancomycin was delivered to patients daily by CI than II, and therapeutic drug monitoring costs were similar. After controlling for differences in vancomycin dose by case matching with propensity scores, mean vancomycin levels were $20.0 \pm 3.8 \mu\text{g}/\text{mL}$ for CI, vs $14.8 \pm 4.4 \mu\text{g}/\text{mL}$ for II ($P < .001$). CI dosing resulted in similar levels with or without CVVH, whereas in II dosing, CVVH appeared to significantly decrease vancomycin levels. Although CI dosing was associated with higher vancomycin levels in general and fewer levels of $<10 \mu\text{g}/\text{mL}$, significant nephrotoxicity or neutropenia was not observed. Fifty-seven patients (33.3%) developed bacteremia, and 106 Gram-positive bacteria were recovered, including 63 *Staphylococcus aureus*. Recurrent bacteremia while receiving vancomycin was infrequent. The 90th percentile minimum inhibitory concentration (MIC_{90}) for vancomycin of 36 available *S. aureus* isolates tested by broth microdilution was 1.5 $\mu\text{g}/\text{mL}$. CI produced more frequent therapeutic vancomycin levels and less frequent subtherapeutic levels compared to II. However, therapeutic vancomycin levels were achieved infrequently by either method of dosing. Given equivalent therapeutic drug monitoring costs and the lack of a clear clinical benefit, the role of CI dosing remains to be defined in spite of practical and theoretical advantages, particularly when administered in the setting of CVVH. (J Burn Care Res 2012;33:e254-e262)

Infection remains a leading cause of death among burn survivors beyond 72 hours of initial injury.¹ Vancomycin is often an empiric antibiotic of choice in

this population as *Staphylococcus aureus* is the most frequently isolated Gram-positive organism.² However, the pharmacokinetics of vancomycin are significantly

From the *Infectious Disease Service, Brooke Army Medical Center, Fort Sam Houston, Texas; †Uniformed Services University of the Health Sciences, Bethesda, Maryland; ‡Department of Pharmacy Practice, University of the Incarnate Word Feik School of Pharmacy, San Antonio, Texas; §Burn Intensive Care Unit, United States Army Institute of Surgical Research, Fort Sam Houston, Texas; and ||Infectious Disease Clinical Research Program, Uniformed Services University of the Health Sciences, Bethesda, Maryland.

Disclaimer: The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army, Department

of Defense or the U.S. Government. This work was prepared as part of their official duties and, as such, there is no copyright to be transferred.

Address correspondence to Kevin S. Akers, MD, Infectious Disease Service, San Antonio Military Medical Center, Brooke Army Medical Center, 3551 Roger Brooke Drive, Fort Sam Houston, Texas 78234.

Copyright © 2012 by the American Burn Association.
1559-047X/2012

DOI: 10.1097/BCR.0b013e31825042fa

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 01 NOV 2012		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE Serum Vancomycin Levels Resulting From Continuous or Intermittent Infusion in Critically Ill Burn Patients With or Without Continuous Renal Replacement Therapy				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Akers K., Cota J., Chung K. K., Renz E. M., Mende K., Murray C. K.,				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 9	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

altered because of the abnormal physiology of burn victims.^{3,4} Increases in the apparent volume of distribution, metabolic, and nonmetabolic clearance have been observed.⁵ As a result, standard vancomycin doses deemed appropriate for nonburned patients may be inadequate for patients with burn injury.

Intravenous vancomycin can be delivered as either a continuous (CI) or an intermittent infusion (II). Recent guidelines directed at adult, nonburned patients recommend II vancomycin 15 to 20 mg/kg every 8 to 12 hours and suggest no clinical advantage with CI dosing.^{4,6} It is unknown whether CI vancomycin results in comparable outcomes in a burn population, and both methods of dosing were used in our facility during the periods examined in this study. This examination afforded us an opportunity to compare the effects of CI vs II vancomycin on clinical outcomes, toxicity, and attainment of recommended serum concentrations in critically ill burn patients. These outcomes were also assessed in a cohort of our patients who were concurrently receiving high-dose CVVH as limited data were available on the outcome of this continuous renal replacement modality on vancomycin pharmacokinetics.

MATERIALS AND METHODS

Study Design

This retrospective cohort study evaluated the use of CI vs II vancomycin therapy on clinical outcomes in critically ill burn patients. Electronic medical records were retrospectively reviewed for all patients admitted to the United States Army Institute of Surgical Research burn intensive care unit from 2006 to 2009 with vancomycin levels recorded in the clinical record. Dosing was considered continuous if the vancomycin was infused without scheduled interruption during multiple 24-hour periods, as opposed to being administered as multiple divided doses per 24-hour period (ie, II). Typical practice in our intensive care unit was to initiate vancomycin therapy at a dose of 1 g every 8 hours for II, or 3 g per 24 hours for CI. Dosing decisions were made by the clinical treatment team, a multidisciplinary care team that included burn surgeons, critical care physicians, and clinical pharmacists. Although therapeutic drug monitoring guidelines for vancomycin were unavailable during this period for infections other than pneumonia, dose adjustment to achieve trough levels of 15 to 20 $\mu\text{g/mL}$, in accordance with the 2005 American Thoracic Society/Infectious Disease Society of America joint recommendation for hospital-acquired pneumonia,⁷ was generally followed for burn patients with nonpneumonia infections out of concern for increased vancomycin clearance in this population. When CI was used,

steady-state levels of 20 to 25 $\mu\text{g/mL}$ were targeted following the practice of a randomized multicenter clinical trial of CI vancomycin.⁸

Patients were excluded from analysis if they were less than 18 years of age, pregnant, admitted for other than a primary thermal burn injury, or had only a single vancomycin level available. Vancomycin doses and serum levels resulting from treatment by CI or II, with or without high-dose CVVH, were considered, and patients contributed data only once to the analysis. For patients who received multiple treatment courses with vancomycin, the treatment course during which high-dose CVVH therapy was concurrently received was selected for inclusion to ensure adequate data. The study was approved by the Institutional Review Board.

Data Collection

The total daily vancomycin dose, CVVH treatment parameters, age, sex, and TBSA burned were obtained from electronic records. To assess toxicities of vancomycin therapy, serum creatinine and absolute numbers of total leukocytes, neutrophils, and platelets were recorded. Trough values after at least three doses (for II) or plateau levels after at least 24 hours (for CI) were considered. Vancomycin levels were determined in the course of routine clinical care by the automated fluorescence polarimetry method of the clinical laboratory. To develop a representative impression of infecting organisms in our facility, agents of Gram-positive bacteremia in the included patients were obtained from the electronic record within 30 days (before or after) of the vancomycin treatment course recovered from blood cultures. Vancomycin MICs were determined by the clinical laboratory using the Vitek-2 instrument (bioMérieux, Durham, NC). Available isolates of *S. aureus* were further examined for vancomycin susceptibility using the Phoenix automated microbiology system (Becton, Dickinson & Co., Franklin Lakes, NJ) and by broth microdilution following the methods and interpretive criteria of the Clinical and Laboratory Standards Institute (CLSI). Pulsed-field gel electrophoresis was performed to characterize the clonal relationships of the isolates, as previously described.⁹ Costs associated with vancomycin therapeutic drug monitoring were assessed using laboratory cost data (in 2011 dollars) obtained from the hospital clinical laboratory.

Outcomes

Differences in 14-day, 28-day, overall in-hospital, and attributable mortality were assessed in patients receiving continuous vs intermittent vancomycin therapy. In addition, recurrent bacteremia and nephrotoxicity (defined according to indices previously

associated with increased mortality¹⁰: ≥ 0.5 mg/dL or $\geq 50\%$ increase in serum creatinine) from start to end of vancomycin therapy were evaluated. Glomerular filtration rate (GFR) was estimated using the Cockcroft-Gault formula. For patients receiving CVVH therapy, nephrotoxicity was defined as having a urine output < 0.3 mL/kg/day. The effect of vancomycin on granulocytes and platelets was evaluated by calculating the difference in total white blood cells, neutrophils, and platelets at the beginning and end of the therapeutic course. An absolute neutrophil count (ANC) of ≤ 500 cells/ μ L was used to define neutropenia.¹¹ As a standardized definition for drug-induced thrombocytopenia is lacking,¹² we defined thrombocytopenia as $< 75 \times 10^3$ platelets/ μ L. Frequencies of achieving "therapeutic" vancomycin levels were compared for those receiving CI (therapeutic range: plateau 20–25 μ g/mL) vs II (therapeutic range: trough 15–20 μ g/mL). As previous studies in our institution identified a mean CVVH dose of 50 mL/kg/hr,¹³ the effect of CVVH therapy at rates above and below this threshold on vancomycin levels was also examined.

Statistical Analysis

Dichotomous variables were compared using the χ^2 test. Continuous variables were tested for normality using the Kolmogorov-Smirnov test, and compared using the Student's *t*-test or Mann-Whitney *U* tests, as appropriate. To normalize differences in the mean vancomycin dose (in grams) delivered to patients by CI vs II, binary logistic regression was used to determine a propensity score reflecting the probability of having received vancomycin by CI, using as covariates age, sex, initial TBSA burned, average daily vancomycin dose, and survival. Cases were matched with controls using a supplemental software algorithm freely available in the public domain.¹⁴ The Wilcoxon

rank-sum test was used to compare mean leukocyte, neutrophil, and platelet counts at the beginning and end of vancomycin therapy. All calculations were performed using Statistical Package for Social Sciences for Windows, version 16.0 (SPSS, Inc., Chicago, IL) except for power calculation, which was performed using PASS 2000 (NCSS, Kaysville, UT).

RESULTS

Patient and Infection Characteristics

During the 4-year period studied (2006–2009), 4235 vancomycin levels (troughs for IIs, or steady-state levels for CIs) were measured in 310 patients. During this period, which included peak workloads of combat casualty care, CI vancomycin dosing was used as a means to reduce the burden and complexity of care for the nursing staff to maximize patient care capabilities in a busy burn critical care ward. Therapeutic drug monitoring for vancomycin was used to assure the adequacy of serum levels. The associated laboratory monitoring cost (calculated at \$12.76 per assay in 2011 dollars) was \$54,039.

A total of 2110 vancomycin levels from 171 patients were included in the analysis after excluding patients according to the previously described criteria. Age, sex, initial percentage of TBSA, body weight at initiation of therapy, serum creatinine at the beginning of therapy, proportion receiving high-dose CVVH, CVVH dose, and estimated GFR were not significantly different between patients who received CI and those who did not (Table 1). Those treated with CI received more vancomycin than patients given II (29.5 ± 11.8 vs 26.2 ± 8.6 mg/kg/day, $P = .02$). Median (25–75% interquartile range) therapeutic drug monitoring costs were not significantly different between those receiving CI compared to II (\$114.84 [\$63.80–\$204.16] vs \$114.84 [\$76.56–\$216.92], $P = .91$).

Table 1. Baseline patient characteristics

	Continuous (N = 90)	Intermittent (N = 81)	P
Age (mean \pm SD yr)	40.8 \pm 19.8	35.6 \pm 17.2	.20
Male (%)	91.1	90.1	1.00
Initial TBSA (%)	38.8 \pm 22.4	43.0 \pm 23.6	.24
Body weight at start of therapy (kg)	89.4 \pm 20.8	91.3 \pm 21.5	.66
Mean vancomycin dose (g/day)	2.50 \pm 0.72	2.29 \pm 0.63	.02
Mean vancomycin received (mg/kg/day)	29.5 \pm 11.8	26.2 \pm 8.6	.02
Mean serum creatinine (mg/dL)	0.99 \pm 0.39	0.97 \pm 0.40	.44
Receiving high-dose CVVH (%)	22 (24.4%)	11 (13.6%)	.11
Mean high-dose CVVH (mL/kg/hr)	50.8 \pm 20.9	50.7 \pm 21.7	.99
Estimated GFR (mL/min)	90.8 \pm 39.2	102.5 \pm 49.9	.14

CVVH, continuous venovenous hemofiltration; GFR, glomerular filtration rate.

Bacteriology and MIC Results

Fifty-seven of 171 patients (33.3%) had Gram-positive bacteremia, with 106 isolates recovered from 87 cultures in 57 patients. Sixty-three isolates (59.4%) were *S. aureus*, of which 27 (25.5%) were methicillin-resistant *S. aureus* (MRSA). Thirteen isolates (12.3%) were coagulase-negative *Staphylococcus*, 13 (12.3%) were *Enterococcus faecium*, five (4.7%) were *Enterococcus faecalis*, four (3.8%) were *Streptococcus pneumoniae*, two (1.9%) were *Streptococcus viridans*, two (1.9%) were *Streptococcus agalactiae*, two (1.9%) were nonenterococcal Group D *Streptococci*, one (0.9%) was *Streptococcus mutans*, and one (0.9%) was an unidentified *Enterococcus* species. Organisms having MIC ≥ 2 $\mu\text{g/mL}$ (as measured by the Vitek-2 instrument) included 15 *S. aureus* (23.8%), 10 coagulase-negative *Staphylococcus* (76.9%), two *E. faecalis* (40%), and one *E. faecium* (8%). Although follow-up blood culturing was not performed in a standardized fashion, recurrence of Gram-positive bacteremia after beginning vancomycin therapy was observed in only 10 patients (17.5%). Four of these (7.0%) had recurrent methicillin-susceptible *S. aureus* (MSSA), two (3.5%) had MRSA, and four (7.0%) had vancomycin-susceptible enterococci. Only one of these (a vancomycin-susceptible *E. faecalis*) occurred in a patient receiving CVVH therapy. Two isolates of MSSA and one vancomycin-susceptible *E. faecium* occurred in patients receiving intermittent vancomycin infusion, with the remaining seven isolates occurring after initiation of CI therapy. Five isolates of coagulase-negative *Staphylococcus* were recovered after starting vancomycin therapy, which, in view of their single occurrence in each patient, likely reflected blood culture contamination.

Vancomycin MIC results were available from the clinical laboratory for 60 of the 63 *S. aureus* isolates, with three isolates categorized as susceptible to vancomycin by disk diffusion. MIC₅₀, MIC₉₀, and percentage susceptible to vancomycin were 1 $\mu\text{g/mL}$, 2 $\mu\text{g/mL}$, and 100%, respectively, using the Vitek-2 instrument, and were confirmed with the Phoenix automated microbiology system in 36 *S. aureus* isolates available for further testing. Broth microdilution testing of these isolates determined vancomycin MIC₅₀ and MIC₉₀ to be 0.75 and 1.5 $\mu\text{g/mL}$, respectively. Pulsed-field gel electrophoresis typing data were available for 17 isolates and revealed five distinct strains: 11 USA100, one USA200, three USA300, and two unique strains. Vancomycin MICs did not rise among serial isolates recovered from individual patients.

Clinical Outcomes

There were no significant differences between recipients of CI or II of vancomycin in 14-, 28-day mortality, or overall in-hospital mortality (Table 3). There were no deaths among 15 patients with a mean vancomycin level <10 $\mu\text{g/mL}$, in contrast to 46 deaths in 156 patients (29.5%) with mean vancomycin level >10 $\mu\text{g/mL}$. Attributable mortality could not be conclusively determined as a result of the multifactorial nature of insults to patients who died, who often had simultaneous Gram-negative and/or invasive fungal infections along with severe burn injury and multiple organ system failure.

To adjust for unequal vancomycin dosing in patients receiving CI vs II, a case-control analysis was performed using a matching algorithm based on the probability of subjects having received CI vancomycin, reflected in a propensity score. Forty-four cases were matched with 44 controls using this algorithm, and outcomes were not statistically different. For similar vancomycin doses (intermittent dosing, 26.6 ± 7.7 mg/kg/day; CI dosing, 25.2 ± 7.1 mg/kg/day, $P = .37$), recipients of CI dosing had higher mean vancomycin levels (14.8 ± 4.4 $\mu\text{g/mL}$ vs 20.0 ± 3.8 $\mu\text{g/mL}$, $P < .001$). CI recipients had significantly fewer levels <10 $\mu\text{g/mL}$ compared to II recipients ($5.9 \pm 9.2\%$ vs $33.6 \pm 25.8\%$, $P < .001$).

A subset analysis stratifying patients on the basis of the clinical indication for vancomycin dosing (Gram-positive bacteremia, sepsis without confirmed Gram-positive bacteremia, or pneumonia) was performed, revealing a statistically significant increase in mortality among patients with sepsis dosed empirically by CI vancomycin (Table 2). This increase occurred in spite of a higher mean serum vancomycin level and did not correspond to significant differences in the percentage of TBSA, the use of CVVH, or subsequent identification of Gram-negative bacteremia as the cause of sepsis in this subgroup.

Although follow-up blood culturing was not performed in a standardized fashion, recurrence of Gram-positive bacteremia after beginning vancomycin therapy was observed in only 10 patients. Seven patients receiving CI had recurrent bacteremia (two MSSA, two MRSA, and three vancomycin-susceptible enterococci), with the remaining three recurrences occurring in the II group (two MSSA and one vancomycin-susceptible *E. faecium*). Five isolates of coagulase-negative *Staphylococcus* were recovered after starting vancomycin therapy, which likely reflected blood culture contamination caused by their single occurrence in each patient.

Toxicity Associated With Vancomycin Therapy

Nephrotoxicity and thrombocytopenia were not different for patients receiving CI vs II vancomycin (Table 3). For platelets, the interquartile ranges and medians for the overall population were 25th percentile, 7000 to 129,000 cells/ μ L (median 66,000 cells/ μ L); 50th percentile, 130,000 to 281,000 cells/ μ L (median 208,000 cells/ μ L); 75th percentile, 282,000 to 444,000 cells/ μ L (median 377,000 cells/ μ L); 100th percentile, 451,000–1,334,000 cells/ μ L (median 451,000 cells/ μ L). The lowest platelet count at the end of therapy was 7000 cells/ μ L and was below 75,000 cells/ μ L in 27 patients (range, 7000 to 73,000 cells/ μ L). The frequency of thrombocytopenia did not differ significantly according to vancomycin dosing strategy, even when the definition was broadened from 75,000 to 150,000 platelets/ μ L (Table 3, data not shown). The lowest ANC at the end of therapy was 1800 cells/ μ L. No patients

had neutropenia (defined as <500 neutrophils/ μ L). Overall, the number of total leukocytes and neutrophils were unchanged during vancomycin therapy, and platelet counts rose significantly during therapy by either method of dosing (Table 4).

As the duration of vancomycin therapy has been associated with toxicity, we compared toxicity outcomes in 33 patients treated for more than 14 days with 138 patients treated for <14 days. Those treated for >14 days had a lower estimated GFR compared to those receiving shorter courses (78.8 ± 28.2 vs 100.9 ± 47.2 mL/min, $P = .002$). This was also true for the subset of patients receiving CVVH (79.8 ± 29.0 vs 99.2 ± 44.2 mL/min, $P = .04$). Among patients who did not receive CVVH, those treated with vancomycin for >14 days had a slightly higher mean vancomycin level (19.1 ± 4.1 vs 17.0 ± 5.1 μ g/mL, $P = .04$) and higher estimated therapeutic drug monitoring cost ($\$338.14 \pm \168.34 vs $\$129.14 \pm \68.4 , $P < .001$). Only three

Table 2. Outcomes of continuous vs intermittent vancomycin dosing according to clinical indication

	Continuous Infusion	Intermittent Infusion	P
Gram-positive Bacteremia (N = 45, 26.3%)			
N	25	20	
CVVH	2 (8.0%)	1 (5.0%)	1.00
Mortality (N)	4 (16.0%)	5 (25.0%)	.48
Average %TBSA	40.1 ± 17.4	46.2 ± 27.3	.39
Gram-negative bacteremia or candidemia (%)	4 (16.0%)	9 (45.0%)	.05
Vancomycin dose (mean \pm SD, mg/kg/day)	36.7 ± 16.8	25.2 ± 10.8	.012
Total vancomycin dose (mean \pm SD, g/d)	2.93 ± 0.70	2.12 ± 0.74	.001
Serum vancomycin level (mean \pm SD μ g/mL)	19.3 ± 3.2	16.1 ± 5.6	.03
Duration of therapy (mean \pm SD, d)	12.4 ± 11.8	13.3 ± 12.4	.81
Sepsis without proven Gram-positive bacteremia (N = 38, 22.8%)			
N	20	18	
CVVH	11 (55.0%)	8 (44.4%)	.75
Mortality (N)	14 (70.0%)	3 (16.7%)	.001
Average %TBSA	46.5 ± 23.6	45.8 ± 21.1	.93
Gram-negative bacteremia or candidemia (%)	9 (45.0%)	8 (44.4%)	1.00
Vancomycin dose (mean \pm SD, mg/kg/d)	28.5 ± 7.6	23.9 ± 7.6	.07
Total vancomycin dose (mean \pm SD, g/d)	2.44 ± 0.74	2.16 ± 0.50	.17
Serum vancomycin level (mean \pm SD μ g/mL)	21.2 ± 4.2	17.0 ± 5.1	.009
Duration of therapy (mean \pm SD, d)	8.7 ± 5.9	6.7 ± 5.3	.29
Pneumonia (N = 39, 22.8%)			
N	20	19	
CVVH	5 (25.0%)	0 (0.0%)	.05
Mortality (N)	7 (35.0%)	4 (21.1%)	.48
Average %TBSA	34.5 ± 25.4	36.6 ± 19.5	.77
Gram-negative bacteremia or candidemia (%)	4 (20.0%)	6 (31.6%)	.48
Vancomycin dose (mean \pm SD, mg/kg/d)	26.8 ± 9.3	27.0 ± 9.2	.93
Total vancomycin dose (mean \pm SD, g/d)	2.3 ± 0.7	2.3 ± 0.7	.96
Serum vancomycin level (mean \pm SD μ g/mL)	22.0 ± 3.9	15.6 ± 4.3	$<.001$
Duration of therapy (mean \pm SD, d)	13.5 ± 11.1	11.2 ± 7.7	.47

CVVH, continuous venovenous hemofiltration.

Table 3. Outcomes and toxicity parameters in patients receiving continuous vs intermittent vancomycin infusions

	All Patients No. (%)			Non-CVVH Patients No. (%)			Case Matched* No. (%)		
	Continuous (n = 90)	Intermittent (n = 81)	P	Continuous (n = 68)	Intermittent (n = 70)	P	Continuous (n = 44)	Intermittent (n = 44)	P
14-day mortality	9 (10.0)	5 (6.2)	.41						
28-day mortality	17 (18.9)	9 (11.1)	.20						
In-hospital mortality	29 (32.2)	17 (21.0)	.14	13 (19.1)	14 (20.0)	.90	9 (20.4%)	8 (18.2%)	
≥50% SCr increase	7 (7.8)	13 (16.0)	.10	7 (10.4%)	13 (18.6%)	.23	7 (15.9%)	10 (22.7%)	.76
≥0.5 mg/dL SCr increase at end of therapy	6 (6.7%)	12 (14.8%)	.13	6 (8.8%)	12 (17.1%)	.21	4 (9.1%)	7 (15.9%)	.52
≥0.5 mg/dL SCr increase, any time during therapy	18 (20.0%)	20 (24.7%)	.47	15 (22.1%)	16 (22.9%)	1.00	9 (20.5%)	10 (22.7%)	1.00
Estimated GFR [‡] (mL/min)	90.8 ± 39.2	102.5 ± 49.9	.14	90.8 ± 35.2	98.2 ± 47.4	.36	93.2 ± 36.7	89.3 ± 40.0	.69
Thrombocytopenia [†]	16 (17.8)	11 (13.6)	.53	5 (7.4)	5 (7.1)	.96	3 (6.8%)	2 (4.5%)	1.00

* Case-control matching based on propensity score reflecting probability of having received continuous-infusion vancomycin.

[†] Total platelet count <75 cells/μL × 1000.

[‡] GFR, glomerular filtration rate estimated using the Cockcroft-Gault method.

CVVH, continuous venovenous hemofiltration; GFR, glomerular filtration rate; SCr, serum creatinine.

patients receiving vancomycin >14 days received CVVH, thus limiting the analysis for this group. There were no statistically significant differences in white blood cell, ANC, or platelets (either absolute or as a percentage change during therapy) between patients receiving >14 days vs ≤14 days vancomycin therapy (data not shown).

Vancomycin Levels and Effect of High-Dose CVVH

Among patients receiving CVVH therapy, vancomycin therapy was initiated in one patient at 4 g every 6 hours (48 mg/kg), in seven patients every 8 hours (33.9 ± 4.9 mg/kg), and in three every 12 hours (27.1 ± 8.7 mg/kg). The remaining patients, treated by CI dosing, received initial doses of 31.7 ± 10.4 mg/kg administered in the span of 24 hours.

Burn patients receiving CI had levels within the therapeutic range more frequently than those receiving II (Table 5). There was no difference in dosing

methods with respect to the frequency of levels occurring above or below the therapeutic range. CI recipients had vancomycin levels <10 μg/mL, less often than II recipients; however, CI was significantly associated with levels >25 μg/mL more frequently than II recipients. However, this did not appear to result in increased nephrotoxicity.

Thirty-three patients received treatment with high-dose CVVH during vancomycin therapy. Twenty were treated using the NxStage system with a CAR-500 polyethersulfone filter having a 1.5 m² surface area (NxStage Medical Inc., Lawrence, MA). Thirteen were treated using the Prismaflex system with a HF1400 polyarylethersulfone filter having a 1.4 m² surface area (Gambro, Lakewood, CO). The average hemofiltration rate among all high-dose CVVH recipients on the first day of therapy was 50.8 ± 21.1 mL/kg/hr. Nineteen patients were treated with an initial hemofiltration rate <50 mL/kg/hr, whereas 14 were treated initially ≥50 mL/kg/hr (mean hemofiltration

Table 4. Laboratory indicators of bone marrow toxicity during therapy with continuous or intermittent vancomycin infusions

	Start of Therapy	End of Therapy	P
Continuous infusion			
Median (IQR) leukocytes (× 1000/μL)	10.6 (8.4–17.5)	12.2 (8.4–18.8)	.22
Median (IQR) neutrophils (× 1000/μL)	9.1 (6.7–14.8)	9.9 (6.4–16.5)	.33
Median (IQR) platelets (× 1000/μL)	176 (101–271)	236 (108–417)	.001
Intermittent infusion			
Median (IQR) leukocytes (× 1000/μL)	11.5 (8.4–16.5)	12.2 (8.9–16.5)	.29
Median (IQR) leutrophils (× 1000/μL)	8.9 (6.5–12.9)	9.9 (6.9–14.2)	.25
Median (IQR) platelets (× 1000/μL)	181 (113–293)	320 (155–478)	<.001

IQR, interquartile range.

Table 5. Frequency of vancomycin levels among patients receiving continuous or intermittent infusions, with or without concurrent CVVH therapy

	Non-CVVH Patients			CVVH Patients		
	Continuous N = 68	Intermittent N = 70	P	Continuous N = 22	Intermittent N = 11	P
Within range* (%)	30.7 ± 19.9	22.6 ± 17.6	.01	30.0 ± 20.3	36.6 ± 17.5	.35
Below range* (%)	50.0 ± 26.7	55.4 ± 28.2	.25	45.1 ± 29.6	19.0 ± 16.4	.01
Above range* (%)	19.3 ± 21.7	22.0 ± 21.8	.46	24.9 ± 24.1	44.4 ± 24.4	.03
<10 µg/mL (%)	4.9 ± 8.0	33.9 ± 26.5	<.01	3.5 ± 10.6	3.0 ± 6.8	.88
10–15 µg/mL (%)	13.5 ± 11.9	20.5 ± 15.6	<.01	16.0 ± 18.8	16.1 ± 16.2	.99
15–20 µg/mL (%)	32.3 ± 20.8	22.6 ± 17.6	<.01	25.6 ± 20.8	36.6 ± 17.5	.14
20–25 µg/mL (%)	30.7 ± 19.9	13.7 ± 15.6	<.01	30.0 ± 20.3	14.1 ± 18.3	.03
>25 µg/mL (%)	19.3 ± 21.7	9.9 ± 12.6	<.01	24.9 ± 24.1	30.3 ± 18.3	.52

* Therapeutic range: plateau level of 20 to 25 µg/mL for continuous infusion and trough level of 15 to 20 µg/mL for intermittent infusion.
CVVH, continuous venovenous hemofiltration.

rate 35.6 ± 9.0 mL/kg/hr vs 71.4 ± 13.8 mL/kg/hr, $P < .001$). Replacement fluids on the first day of therapy were given at 3.3 ± 0.9 L/hr and 5.8 ± 1.4 L/hr in these groups, respectively ($P < .001$).

The influence of high-dose CVVH therapy on serum vancomycin levels was examined (Table 5). The average daily vancomycin doses from CI or CI were equivalent in patients who received concurrent high-dose CVVH therapy (26.4 ± 6.4 vs 23.8 ± 6.8 mg/kg/day; $P = .30$). The average hemofiltration rates were nearly identical in these groups. CI in patients receiving high-dose CVVH was associated with more frequent supratherapeutic levels compared to CI (Table 5). Levels of 10 to 15 µg/mL and 15 to 20 µg/mL were achieved equally as often between the two dosing methods. The frequency of achieving stratified vancomycin levels did not vary significantly for patients who received CVVH therapy with hemofiltration rate above vs below 50 mL/kg/min (data not shown).

DISCUSSION

Both the vancomycin therapeutic drug monitoring consensus review⁶ and the MRSA guidelines¹⁵ recommend the use of CI vancomycin over CI. However, randomized studies in nonburn patients have reported that CI vancomycin is associated with similar outcomes, decreased variability of the area under the 24 hour time-concentration curve (AUC_{24}), lower doses, reduced cost, and more rapid target level attainment compared to intermittent dosing.⁸ In this study, we found no difference in overall clinical outcomes or toxicity in critically ill burn patients receiving CI vancomycin, and therapeutic drug monitoring costs were equivalent between the dosing methods. This calls into question the cost-benefit

relationship of therapeutic drug monitoring for vancomycin in terms of improving efficacy or limiting toxicity in critically ill burn patients.

Burn patients who received CI vancomycin in our study more frequently had levels in the therapeutic range and were less likely to have serum levels <10 µg/mL—a threshold suggested to prevent the emergence of subpopulations of *S. aureus* with reduced vancomycin susceptibility by recent guidelines. The overall higher vancomycin exposure associated with CI may have been the result of more convenient dosing leading to fewer treatment interruptions in the complex environment of care for these critically ill patients. Although CI delivery was also associated with more frequent levels >25 µg/mL, an association between CI dosing and adverse renal outcomes was not evident in our data (although our study lacked sufficient power for this endpoint). The use of CI vancomycin in a burn population could lead to more consistent AUC/MIC ratios, which has been proposed as the therapeutic target in published guidelines⁶ for isolates of MRSA with higher vancomycin MICs. However, the desire to comply with guideline-recommended target levels should be balanced against the increased probability of achieving supratherapeutic vancomycin levels when using CI dosing, which could potentially enhance the risk of toxicity.¹⁶

We observed a significantly increased mortality rate in a subgroup of patients receiving vancomycin empirically by CI for clinical sepsis whose blood cultures were negative for Gram-positive organisms. The reasons for this are not clear, as this finding did not correlate with the initial percentage of TBSA, the use of CVVH, or the subsequent recovery of Gram-negative organisms in blood cultures during the septic episode.

Our results raise concern on the adequacy of vancomycin therapy overall in severely burned patients regardless of the method of infusion. Notably, vancomycin levels of 20 to 25 $\mu\text{g/mL}$ (for CI) or 15 to 20 $\mu\text{g/mL}$ (for II) were achieved roughly one third of the time or less, thus treatments frequently failed to meet guideline-recommended targets,⁶ given the vancomycin MIC_{90} of 1.5 $\mu\text{g/mL}$ in the isolates of *S. aureus*. Nevertheless, recurrence of *S. aureus* bacteremia after beginning vancomycin therapy was infrequent, observed in only 10.5% of patients with Gram-positive bacteremia although follow-up cultures were not obtained in every case.

Patients who were administered II received an average vancomycin dose of 2.3 g per day (26.2 mg/kg/day), but fell below a trough of 15 $\mu\text{g/mL}$ more than half of the time. More aggressive vancomycin doses >4 g per day would likely be required to maintain troughs 15 to 20 $\mu\text{g/mL}$ (predicted $\text{AUC}_{24} > 360\text{--}480 \mu\text{g}\cdot\text{hr/mL}$)¹⁷ for our burn population. This is concerning because retrospective studies evaluating II vancomycin in intensive care unit patients have suggested >20% predicted probability of nephrotoxicity in patients with initial trough values >10 $\mu\text{g/mL}$ or in patients receiving total daily doses $\geq 4 \text{ g/day}$.^{18,19} In contrast, a wider therapeutic index may be observed with CI vancomycin since increased nephrotoxicity has been observed with steady-state vancomycin levels $\geq 28 \mu\text{g/mL}$ in patients with concurrent risk factors.¹⁶ Theoretically, vancomycin levels of 16.7, 25, and 33.4 $\mu\text{g/mL}$ would maintain an AUC/MIC ratio ≥ 400 when the MIC is 1.0, 1.5, or 2.0 $\mu\text{g/mL}$, respectively, assuming constant vancomycin levels over 24 hours. These target steady-state vancomycin levels may be achieved in critically ill nonburn patients with lower total daily doses of vancomycin (<4 g/day), if administered via CI.²⁰ No patient had absolute leukopenia or neutropenia, and few in this group had evidence of renal impairment attributable to vancomycin. Although thrombocytopenia did occur in some patients, mean platelet counts significantly increased overall during vancomycin therapy with both methods of infusion.

Our study also evaluated the influence of high-dose CVVH (average effluent rate 50 mL/kg/hr) on target attainment for intermittent and CI vancomycin since most continuous renal replacement therapy (CRRT) effluent rates are much lower (20–35 mL/kg/hr).²¹ CI administration of antibiotics may be preferred in patients receiving CRRT because of the variable removal of drug that occurs when replacement parameters are changed.²² In addition, continuous administration allows for rapid adjustment of infusion

rates based on predicted drug removal or mechanical CRRT failures. There was no difference in frequency of therapeutic vancomycin levels between CI and II. However, II recipients had supratherapeutic levels almost half of the time. Exposure to excessive concentrations may be prolonged if a CRRT line clots soon after administration of a bolus dose of antibiotic. It is unclear whether the excessive vancomycin exposure in the intermittent group was because of CRRT mechanical failures or the use of aggressive dosing (26.4 mg/kg/day). Recommendations for intermittent vancomycin dosing in CVVH with lower ultrafiltration rates ($\sim 20 \text{ mL/kg/hr}$) is generally $\leq 15 \text{ mg/kg}$ every 24 hours. The recommended dose of intermittent vancomycin in high-dose CVVH may therefore be $\sim 20 \text{ mg/kg}$ every 24 hours. Interestingly, the CI dose of vancomycin of 23.8 mg/kg/day in burn patients receiving high-dose CVVH resulted in subtherapeutic levels. This finding highlights the importance of infusion method when designing initial dosing regimens in patients undergoing CRRT.

Our study has limitations. As a retrospective study, it is vulnerable to many sources of bias, such as the preferential allocation of patients to the CVVH group who were treated with multiple courses of vancomycin, both with and without concurrent CVVH therapy. Although the study was intended to measure our success in meeting the criterion of $\text{AUC/MIC} \geq 400$, the lack of postinfusion peak data prevented actual calculation of the AUC or other standard pharmacokinetic parameters for vancomycin. Hemofiltration rates documented daily in the medical record may have been inaccurate, as they do not always reflect changes implemented at the bedside in response to rapidly changing hemodynamics of critically ill patients. Also, it was not possible to accurately estimate the effect of renal vancomycin clearance in patients receiving CVVH, as an accurate means to assess residual endogenous renal function in the setting of renal replacement therapy was lacking. Finally, the study was underpowered ($\alpha = 0.05$, $\beta = 0.20$) for the endpoints of interest to clinicians. Using the observed data from the entire cohort of 171 patients, post hoc analysis determined the study power to be 0.32 for mortality, up to 0.39 for nephrotoxicity (best power was for estimated GFR), and 0.08 for thrombocytopenia. As no patient met the endpoint for neutropenia, power was estimated at 0.36 assuming an incidence of 10% for CI vs 20% for II. The power inadequacies in this retrospective observational study raise the possibility that significant findings were not observed because of limitations in sample size.

In conclusion, we found that severely burned patients had vancomycin levels within the therapeutic range only 22.6 to 30.7% of the time. We found similar overall clinical outcomes with CI vancomycin dosing, although a subgroup analysis of patients with clinical sepsis but negative blood cultures revealed increased mortality associated with empiric CI vancomycin therapy. Toxicity appeared to be minimal with both methods of dosing despite an increased frequency of vancomycin levels $>25 \mu\text{g/mL}$ in patients who received CI. CI produced more frequent therapeutic vancomycin levels and less frequent subtherapeutic levels compared to II. Given equivalent therapeutic drug monitoring costs and the lack of a clear clinical benefit, the role of CI dosing remains to be defined in spite of practical and theoretical advantages, particularly when administered in the setting of CVVH.

REFERENCES

1. ABA. American Burn Association National Burn Repository 2007 Report, Dataset Version 4.0. 2008.
2. Keen EF 3rd, Robinson BJ, Hospenthal DR, et al. Incidence and bacteriology of burn infections at a military burn center. *Burns* 2010;36:461–8.
3. Garrelts JC, Peterie JD. Altered vancomycin dose vs. serum concentration relationship in burn patients. *Clin Pharmacol Ther* 1988;44:9–13.
4. Rybak MJ, Albrecht LM, Berman JR, Warbasse LH, Svensson CK. Vancomycin pharmacokinetics in burn patients and intravenous drug abusers. *Antimicrob Agents Chemother* 1990;34:792–5.
5. Blanchet B, Jullien V, Vinsonneau C, Tod M. Influence of burns on pharmacokinetics and pharmacodynamics of drugs used in the care of burn patients. *Clin Pharmacokinet* 2008;47:635–54.
6. 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.
7. ATS/IDSA. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388–416.
8. Wysocki M, Delatour F, Faurisson F, et al. Continuous versus intermittent infusion of vancomycin in severe Staphylococcal infections: prospective multicenter randomized study. *Antimicrob Agents Chemother* 2001;45:2460–7.
9. Murray CK, Holmes RL, Ellis MW, et al. Twenty-five year epidemiology of invasive methicillin-resistant *Staphylococcus aureus* (MRSA) isolates recovered at a burn center. *Burns* 2009;35:1112–7.
10. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005;16:3365–70.
11. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. *Ann Intern Med* 2007;146:657–65.
12. Priziola JL, Smythe MA, Dager WE. Drug-induced thrombocytopenia in critically ill patients. *Crit Care Med* 2010;38(6 Suppl):S145–54.
13. Chung KK, Juncos LA, Wolf SE, et al. Continuous renal replacement therapy improves survival in severely burned military casualties with acute kidney injury. *J Trauma* 2008;64(2 Suppl):S179–85; discussion S185–7.
14. Painter J. Propensity score matching via SPSS. 2004, accessed 21 Nov. 2011; available from: <http://www.unc.edu/~painter>.
15. Liu C, Bayer A, Cosgrove SE, et al. Infectious Diseases Society of America. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis* 2011;52:e18–55.
16. 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.
17. 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.
18. 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.
19. 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.
20. Jeurissen A, Sluys I, Rutsaert R. A higher dose of vancomycin in continuous infusion is needed in critically ill patients. *Int J Antimicrob Agents* 2011;37:75–7.
21. Palevsky PM, Zhang JH, O'Connor TZ, et al. VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008;359:7–20.
22. Moriyama B, Henning SA, Neuhauser MM, Danner RL, Walsh TJ. Continuous-infusion beta-lactam antibiotics during continuous venovenous hemofiltration for the treatment of resistant gram-negative bacteria. *Ann Pharmacother* 2009;43:1324–37.