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Empiric Weight-Based Vancomycin in Intensive Care Unit Patients with Methicillin-Resistant *Staphylococcus Aureus* Bacteremia

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Competing Interests

None: CAA,CAG, KKH, KAH, NAF, SDB, EMM, TB, NMT, RGH

Author's Contributions

CAG, KKH, KAH, SDB, RJB, RGH were involved in the study concept and design.

CAG, CAA, CRF, NMT, RGH were involved in the data analysis and interpretation.

CAG, KKH, KAH, CAA, CRF, NAF, SDB, EMM, TB, RJB, NMT, RGH were involved in the drafting of the manuscript for important intellectual content and had final approval of the manuscript. All authors read and approved the final manuscript.

Abstract

Background—We have conducted previous studies in all hospitalized patients with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia to determine safety and effectiveness of guideline-recommended, weight-based dosing of vancomycin. In these studies, we observed that severely ill patients (Pitt bacteremia score ≥ 4 or ICU patients) were at an increased risk of mortality and/or nephrotoxicity. Therefore, we conducted a subanalysis of the effect of guideline-recommended vancomycin dosing on in-hospital mortality and nephrotoxicity in intensive care unit (ICU) patients with MRSA bacteremia.

Methods—This multicenter, retrospective, cohort study was conducted in a subset of ICU patients from a previous MRSA bacteremia study. Patients were ≥ 18 years old and received ≥ 48 hours of empiric vancomycin from 07/01/2002 to 06/30/2008. We compared the incidence of nephrotoxicity and in-hospital mortality in patients that received guideline-recommended dosing (at least 15 mg/kg/dose) to patients that received non-guideline-recommended dosing of vancomycin. Multivariable generalized linear mixed-effects models were constructed to determine independent risk factors for in-hospital mortality and nephrotoxicity.

Results—Guideline-recommended dosing was received by 34% of patients (n=137). Nephrotoxicity occurred in 35% of patients receiving guideline-recommended dosing and 39% receiving non-guideline-recommended dosing (p=0.67). In-hospital mortality rate was 24% among patients who received guideline-recommended dosing compared with 31% for non-guideline-recommended dosing (p=0.40). Guideline-recommended dosing was not associated with nephrotoxicity (OR 1.10; 95% CI 0.43–2.79) or in-hospital mortality (OR 0.54; 95% CI 0.22–1.36) in the multivariable analysis.

Conclusions—Guideline-recommended dosing of vancomycin in ICU patients with MRSA bacteremia is not significantly associated with nephrotoxicity or in-hospital mortality. However, the 7% absolute difference for in-hospital mortality suggests larger studies are needed.

Keywords

Vancomycin; weight; ICU; MRSA; nephrotoxicity

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia affects 30,000 to 90,000 Americans per year, often requiring intensive care unit (ICU) admission [1, 2]. MRSA now represents approximately 60% of *S. aureus* infections in ICU's in the United States [3]. Vancomycin has remained the drug of choice for invasive MRSA infections for decades; however, multiple statements from professional organizations have changed vancomycin utilization over the past several years. In 2006, the Clinical and Laboratory Standards Institute lowered the accepted susceptibility breakpoint for *Staphylococcus aureus* from 4 mg/L or less to 2mg/L or less [4, 5]. This change was due to increasing vancomycin minimum inhibitory concentrations (MIC) in MRSA and clinical data demonstrate that MIC values ≥ 1 mg/L are associated with worse clinical outcomes [6–9]. The Infectious Disease Society of America (IDSA), American Society of Health-Systems Pharmacists (ASHP), and Society of Infectious Diseases Pharmacists (SIDP) subsequently developed a consensus

document regarding vancomycin dosing. This document recommends using a weight-based approach (15–20 mg/kg/dose IV administered every 8 to 12 hours for most patients) and targeting higher vancomycin trough concentrations (15–20 mg/L) based on pharmacokinetic and pharmacodynamic data [5].

Studies that have evaluated the safety and effectiveness of the guideline-recommended, weight-based vancomycin dosing have primarily focused on clinical strategies to achieve the recommended vancomycin trough concentrations in clinical practice [6, 10, 11]. Our group has also studied empiric guideline-recommended vancomycin dosing in hospitalized patients with MRSA bacteremia; we did not observe a significant association with inpatient mortality or nephrotoxicity [12, 13]. Other factors, including patient age, patient weight, severity of illness, ICU admission, duration of vancomycin use, and vancomycin trough concentrations higher than 20 mg/L were found to be independent risk factors for either inpatient mortality or nephrotoxicity. The safety and effectiveness of empiric guideline-recommended vancomycin dosing has yet to be tested in critically ill patients with MRSA bacteremia. We hypothesize that critically ill patients with MRSA bacteremia who receive empiric guideline-recommended vancomycin dosing will have a decrease in mortality and increase in nephrotoxicity as compared to patients who receive non-guideline-recommended vancomycin doses.

Dose optimization is likely more crucial for ICU patients who are at an increased risk of nephrotoxicity and/or death [10, 11]. Therefore, we conducted this multicenter, retrospective, cohort study in a subset of ICU patients from a previous MRSA bacteremia study to evaluate the effect of the IDSA/ASHP/SIDP guideline-recommended vancomycin dosing on in-hospital mortality and the development of nephrotoxicity in ICU patients with MRSA bacteremia [12].

Materials and Methods

Study location and patients

We included ICU patients with MRSA bacteremia between July 2002 and June 2008 at three hospitals (a 400 bed tertiary hospital, a 350 bed Veteran Affairs hospital, and a 600 bed university hospital). This is a subgroup analysis of a previous retrospective cohort study of hospitalized patients, including both medical ward and ICU patients [12, 13]. None of the study institutions utilized a standardized protocol, so each clinician ordered vancomycin dosing at his/her discretion. Patients 18 years of age were eligible for inclusion if parenteral vancomycin was initiated in the ICU. Duration of vancomycin therapy for at least 48 hours and the presence of MRSA bacteremia, documented by microbiologic records, were required for inclusion in this analysis. Patients were excluded if they were pregnant, had received vancomycin during a prior hospital stay, or had a culture-proven MRSA infection in the previous six months as it was thought they would be at an increased risk of death. Patients were also excluded if they had significant renal dysfunction defined as receipt of dialysis at time of first vancomycin dose or a creatinine clearance (CrCl) of 30 ml/min or less as measured by the Cockcroft-Gault equation [14]. Each study site received approval by its respective institutional review board (VA North Texas Health Care System, Texas Tech University Health Sciences Center, and the University of Texas Health Science

Center, San Antonio) prior to study initiation. Each institutional review board waived the need for informed consent.

Study design and data collection

We conducted a retrospective cohort study comparing in-hospital mortality and nephrotoxicity in ICU patients with MRSA bacteremia treated with guideline-recommended vancomycin dosing to those treated with non-guideline-recommended vancomycin doses.

Study definitions

Receipt of guideline-recommended vancomycin dosing is defined as receiving 30 mg/kg/day or 15 mg/kg/day for CrCl 30–50 ml/min. A creatinine clearance of less than 50 ml/min is used by a leading clinical reference to provide recommendations for drug dosing in renal insufficiency [15]. Patients who received non-guideline-recommended doses were the comparator group. Since this study was focused on empiric dosing, only the vancomycin regimen initially ordered was classified as being guideline-recommended or not. Nephrotoxicity was defined as an increase in serum creatinine (SCr) by greater than 0.5 mg/dl or a 50% increase from baseline on at least two consecutive laboratory tests from the initiation to the completion of vancomycin therapy [9]. In-hospital mortality was defined as patient death occurring within the index hospital stay. Vancomycin trough concentrations were determined using each hospital's assay. Any vancomycin concentration labeled as "trough" was included. Concomitant nephrotoxins were defined as intravenous contrast, aminoglycosides, or vasopressors. Pitt bacteremia score was used to quantify the severity of the illness [16, 17].

Statistical Analysis

Candidate variables selected for consideration in the univariable and the multivariable models were identified *a priori*. To avoid overfitting, we determined that four variables could be included in a multivariable model for mortality and seven variables could be included in a multivariable model for nephrotoxicity. Based on previous studies, we assumed a 30% mortality rate and a 45% nephrotoxicity rate [13, 18, 19]. Based on these assumptions, we determined that 133 patients would be required for the multivariable analyses. Variables examined in the initial univariable analysis included receipt of guideline-recommended vancomycin dosing, patient age, nephrotoxicity, vancomycin trough greater than 15 mg/L, vancomycin duration greater than 15 days, use of concomitant nephrotoxins, baseline serum creatinine, Pitt bacteremia score of 4 or greater, weight of 100kg or greater, hospital length of stay and ICU length of stay, and gender. Univariable associations were explored using either Chi-square or Fisher's Exact tests when appropriate. The vancomycin trough cutoff of 15 mg/L was based on the guideline recommendations (15–20 mg/L) and data that suggest higher trough concentrations are associated with an increased incidence in nephrotoxicity [5, 20]. The Pitt bacteremia score cutoff of 4 or higher was used based on previous literature demonstrating significantly higher sensitivity and specificity for predicting severity of illness [21]. Age greater than 65 was used based on evidence of higher mortality rates in this geriatric population with bacteremia or sepsis [22, 23]. Patients with weight of 100kg or greater were considered to be at high risk because

previous literature has suggested this cut point as an independent risk factor for vancomycin nephrotoxicity [11].

The change-in-estimate method was utilized to select variables for the final multivariable model based on changes in the estimated exposure effect. Any variable demonstrating a 10% change in the exposure effect was determined to be a confounder and kept in the final model [24]. All variables conceptually regarded as biologically reasonable causes of nephrotoxicity or mortality were also considered for inclusion in the multivariable model. A generalized linear mixed-effect model was utilized to identify independent risk factors for nephrotoxicity and mortality. To account for clustering, hospital site was treated as a random effect whereas other covariates were treated as fixed effects. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated for each variable in the multivariable model. All analyses were performed using STATA 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

A total of 798 patients with MRSA bacteremia were evaluated with 137 ICU patients included in the analysis (Table 1). Patients who received guideline recommended dosing weighed less than those who received non-guideline-recommended doses (65 vs. 89 kg; $p<0.001$). Vancomycin was dosed according to guidelines in 34% of the patient population. The cohort was predominantly male (81%) and the baseline characteristics were similar in patients who received guideline-recommended vancomycin dosing compared to those who received non-guideline-recommended doses. As expected, patients in the guideline-recommended dosing group received higher daily doses of vancomycin (31 vs. 21 mg/kg/day; $p<0.001$) and achieved vancomycin troughs of greater than 15 mg/L more frequently (50% vs. 32%; $p=0.04$). The sources of bacteremia were pulmonary (27%), catheter-related (25%), skin and muscle (22%) and other sources (9%). The source of MRSA bacteremia was not identified in 17% of patients.

Nephrotoxicity developed during therapy in 37% of patients, with similar rates between guideline-recommended and non-guideline-recommended dosing (35% vs. 38%; $p=0.67$). Guideline-recommended dosing was not a significant predictor of nephrotoxicity in either the univariable (OR 0.85; 95% CI 0.41–1.78) or multivariable analysis (OR 1.10; 95% CI 0.43–2.79). Patient weight of 100kg or greater, a Pitt bacteremia score of 4 or greater, vancomycin duration greater than 15 days, and the use of concomitant nephrotoxins (aminoglycosides, intravenous contrast, vasopressors) were significantly associated with the development of nephrotoxicity in the univariable analysis (Table 2). Pitt bacteremia score of 4 or greater, patient weight greater than 100kg, patient age greater than 65, and vancomycin duration greater than 15 days were the only factors independently associated with the development of nephrotoxicity in the multivariable analysis (Table 2).

The in-hospital mortality rate was 29%. In the univariable analysis (Table 3), in-hospital mortality was not statistically significantly different for patients who received guideline-recommended dosing and those who received non-guideline-recommended dosing (24% vs. 31% respectively; $p=0.40$). Factors significantly associated with in-hospital mortality in the

univariable analysis were patient age greater than 65 years and the development of nephrotoxicity. Guideline-recommended dosing of vancomycin was not an independent risk factor for in-hospital mortality in the multivariable model (OR 0.54; 95% CI 0.22–1.36). Independent risk factors for in-hospital mortality were patient age greater than 65, the development of nephrotoxicity and a Pitt bacteremia score of 4 or greater (Table 3).

Discussion

This multicenter study evaluated the safety and effectiveness of empiric guideline-recommended vancomycin dosing in ICU patients with MRSA bacteremia. Over a third (37%) of patients experienced nephrotoxicity and more than a quarter (29%) died during their hospital stay. We did not observe a significant relationship between empiric guideline-recommended vancomycin dosing and the development of nephrotoxicity or in-hospital mortality.

The purpose of the new vancomycin dosing recommendations is to achieve higher trough concentrations, in order to reach the target area under the curve (AUC) to MIC ratio (AUC/MIC) for *S. aureus*. Clinical studies regarding whether achieving vancomycin target trough concentrations has a beneficial effect on clinical outcomes have been mixed [12, 18, 20]. The aim of our study was to determine the safety and effectiveness of vancomycin from an empiric dosing perspective. We chose to focus on empiric dosing because clinicians prescribe a vancomycin dosing regimen for a patient with a suspected or documented MRSA infection. The clinician rarely has the vancomycin MIC value at the time of the vancomycin order and does not know for certain what trough that individual patient will achieve, in spite of all of the advances in the field of pharmacokinetics. The 7% absolute decrease in in-hospital mortality seen between guideline-recommended dosing (24%) vs. non-guideline-recommended dosing (31%) is clinically meaningful and deserves further investigation in spite of our inability to detect a statistically significant difference between these rates.

Most studies evaluating the safety of the newly recommended vancomycin dosing strategies have focused on the target trough concentrations. Many of these studies have noted an association between higher trough concentrations and nephrotoxicity [6, 10, 18, 25–27]. Our results focused on empiric dosing suggest that factors other than the vancomycin guideline-recommended dosing are more strongly associated with the development of nephrotoxicity in ICU patients with MRSA bacteremia. This finding suggests that the empiric provision of guideline-recommended vancomycin dosing may pose no additional significant risk to kidney function than non-guideline-recommended vancomycin doses.

The nephrotoxicity rate in our study is similar to other published reports [6, 18, 20, 25]. The independent risk factors for nephrotoxicity in our cohort were a Pitt bacteremia score of 4 or greater, patient weight of 100kg or greater, patient age greater than 65 years, and vancomycin duration greater than 15 days. These risk factors largely coincide with what previous research has found [10, 11, 13, 18, 25]. Studies have also identified a variety of other independent risk factors for nephrotoxicity including concomitant nephrotoxins, decreased renal function, vancomycin trough concentrations, and vancomycin doses of four grams per day or greater. [6, 10, 11, 13, 18, 25]. The severity of illness and duration of

vancomycin therapy in this ICU cohort may have obscured our ability to detect these risk factors described in previous research.

The mortality rate in our study was also similar to others [19]. Independent risk factors for in-hospital mortality were Pitt bacteremia score of 4 or greater, age over 65 years and the development of nephrotoxicity. These independent risk factors have been previously identified [19]. Guideline-recommended vancomycin dosing was not identified as an independent predictor of in-hospital mortality in the present study, which is similar to our previous study of all hospitalized patients [12].

Our study has important limitations. The retrospective design of our study may have been subject to selection bias through unmeasured confounding. A potential advantage of our retrospective design is the possibility of a more realistic evaluation of safety and effectiveness in the clinical setting than a clinical trial. Our study was also limited by the fact that patients greater than 70 kilograms were less likely to receive empiric guideline-recommended vancomycin dosing. This study's timeframe largely occurred prior to the publication of the guidelines. Therefore, doses were chosen by the prescribers at each institution according to the local practice standards of the time. This is likely the reason that only a third of our population was dosed according to current guidelines. Thus in our study when ICU patients received dosing in line with current standards, there was no increase in nephrotoxicity or in hospital mortality. Additional prospective studies or retrospective studies of ICU patients during a period after the publication of the guidelines are needed to confirm our findings. Also, the duration and type of concomitant nephrotoxin were not recorded which may have inhibited our ability to accurately assess the impact of these agents. We did not collect data to classify patients based on the criteria for sepsis, severe sepsis, and septic shock that could have served as another tool in addition to the Pitt bacteremia score to determine the severity of illness of the cohort. Despite these limitations, we were able to adjust for important risk factors for mortality and nephrotoxicity that have been previously identified. The effect of loading doses (25–30 mg/kg) was not assessed, as none of the institutions in our study utilized them. Additional studies specifically evaluating the effect of vancomycin loading doses on clinical outcomes are needed.

Conclusions

Guideline-recommended vancomycin dosing in ICU patients with MRSA bacteremia is not significantly associated with nephrotoxicity or in-hospital mortality. However, the 7% absolute difference in in-hospital mortality between those who received guideline-recommended vancomycin dosing and those that received non-guideline-recommended dosing suggests larger studies are needed. The independent risk factors for nephrotoxicity we found were Pitt bacteremia score of 4 or greater, patient weight of 100kg or greater, patient age greater than 65 years, and vancomycin duration greater than 15 days. In our study, we also determined that Pitt bacteremia score of 4 or greater, age over 65 years and the development of nephrotoxicity were independent risk factors for mortality.

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References

1. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA*. 2007; 298:1763–1771. [PubMed: 17940231]
2. Kuehnert MJ, Hill HA, Kupronis BA, et al. Methicillin-resistant-*Staphylococcus aureus* hospitalizations, United States. *Emerg Infect Dis*. 2005; 11:868–872. [PubMed: 15963281]
3. National Nosocomial Infections Surveillance S. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control*. 2004; 32:470–485. [PubMed: 15573054]
4. Tenover FC, Moellering RC Jr. The rationale for revising the Clinical and Laboratory Standards Institute vancomycin minimal inhibitory concentration interpretive criteria for *Staphylococcus aureus*. *Clin Infect Dis*. 2007; 44:1208–1215. [PubMed: 17407040]
5. 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.
6. Hidayat LK, Hsu DI, Quist R, et al. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. *Arch Intern Med*. 2006; 166:2138–2144. [PubMed: 17060545]
7. 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; 52:3315–3320. [PubMed: 18591266]
8. Sakoulas G, Moise-Broder PA, Schentag J, et al. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. *J Clin Microbiol*. 2004; 42:2398–2402. [PubMed: 15184410]
9. Wang G, Hindler JF, Ward KW, et al. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. *J Clin Microbiol*. 2006; 44:3883–3886. [PubMed: 16957043]
10. Lodise TP, Patel N, Lomaestro BM, et al. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis*. 2009; 49:507–514. [PubMed: 19586413]

11. Lodise TP, Lomaestro B, Graves J, et al. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrob Agents Chemother.* 2008; 52:1330–1336. [PubMed: 18227177]
12. Hall RG 2nd, Giuliano CA, Haase KK, et al. Empiric guideline-recommended weight-based vancomycin dosing and mortality in methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study. *BMC Infect Dis.* 2012; 12:104. [PubMed: 22540223]
13. Hall RG 2nd, Hazlewood KA, Brouse SD, et al. Empiric guideline-recommended weight-based vancomycin dosing and nephrotoxicity rates in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: a retrospective cohort study. *BMC Pharmacol Toxicol.* 2013 In press.
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976; 16:31–41. [PubMed: 1244564]
15. Bennett, WM.; Aronoff, GR.; Golper, TA., et al. *Drug Prescribing in Renal Failure 3rd.* American College of Physicians; Philadelphia, PA: 1994.
16. Chow JW, Fine MJ, Shlaes DM, et al. Enterobacter bacteremia: clinical features and emergence of antibiotic resistance during therapy. *Ann Intern Med.* 1991; 115:585–590. [PubMed: 1892329]
17. Chow JW, Yu VL. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. *Int J Antimicrob Agents.* 1999; 11:7–12. [PubMed: 10075272]
18. Jeffres MN, Isakow W, Doherty JA, et al. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. *Clin Ther.* 2007; 29:1107–1115. [PubMed: 17692725]
19. Pastagia M, Kleinman LC, Lacerda de la Cruz EG, et al. Predicting risk for death from MRSA bacteremia. *Emerg Infect Dis.* 2012; 18:1072–1080. [PubMed: 22709685]
20. Kullar R, Davis SL, Levine DP, et al. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant *Staphylococcus aureus* bacteremia: support for consensus guidelines suggested targets. *Clin Infect Dis.* 2011; 52:975–981. [PubMed: 21460309]
21. Rhee JY, Kwon KT, Ki HK, et al. Scoring systems for prediction of mortality in patients with intensive care unit-acquired sepsis: a comparison of the Pitt bacteremia score and the Acute Physiology and Chronic Health Evaluation II scoring systems. *Shock.* 2009; 31:146–150. [PubMed: 18636041]
22. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. *Crit Care Med.* 2006; 34:15–21. [PubMed: 16374151]
23. Shurland S, Zhan M, Bradham DD, et al. Comparison of mortality risk associated with bacteremia due to methicillin-resistant and methicillin-susceptible *Staphylococcus aureus*. *Infect Control and Hosp Epidemiol.* 2007; 28:273–279. [PubMed: 17326017]
24. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Pub Health.* 1989; 79:340–349. [PubMed: 2916724]
25. Cano EL, Haque NZ, Welch VL, et al. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP Database. *Clin Ther.* 2012; 34:149–157. [PubMed: 22284995]
26. Pritchard L, Baker C, Leggett J, et al. Increasing vancomycin serum trough concentrations and incidence of nephrotoxicity. *Am J Med.* 2010; 123:1143–1149. [PubMed: 21183005]
27. Bosso JA, Nappi J, Rudisill C, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. *Antimicrob Agents Chemother.* 2011; 55:5475–5479. [PubMed: 21947388]

Table 1Baseline characteristics of the cohort^a

Characteristic	Guideline-recommended dosing (n = 46)	Non-guideline recommended dosing (n = 91)	p-value
Male gender (%)	80	81	0.90
Age (years)	56.5 (46, 73)	57 (48, 67)	0.93
Race (%)			0.30
Caucasian	63	76	
African American	13	7	
Other	2	4	
Height (cm)	173 (165, 178)	175 (170, 183)	0.008
Weight (kg)	65 (56, 75)	89 (77, 102)	<0.001
Serum creatinine (mg/dl)	1.0 (0.7, 1.4)	1.0 (0.7, 1.4)	0.91
Pitt Bacteremia Score	3 (2, 4)	3 (1, 6)	0.38
Concomittant nephrotoxins (%)	67	58	0.30
Infection source (%)			0.11
Bloodstream catheter related	30	24	
Pulmonary	24	29	
Skin/muscle	11	27	
Genitourinary	7	4	
Osteomyelitis	0	2	
Central nervous system	0	1	
Gastrointestinal	0	1	
Abscess	0	1	
Other	28	11	
Length of hospital stay (days)	22 (11, 61)	28 (16, 45)	0.96
ICU length of stay (days)	11 (4, 22)	9 (4, 27)	0.78
Initial vancomycin dose (mg/kg/day)	31.2 (26.7, 35.9)	20.6 (15.7, 24.4)	<0.001
Vancomycin 1 gram every 12 hours	33%	44%	0.20
Initial vancomycin trough (mg/dl)	13.9 (9.1, 18.8)	10.6 (7.6, 16.4)	0.10
Initial vancomycin trough > 15 mg/dl (%)	50	32	0.04
Vancomycin duration (days)	15 (8, 21)	13 (8, 19)	0.65

^a = Results are presented as median (interquartile range) unless otherwise noted.

Table 2

Univariable and multivariable analysis of risk factors for nephrotoxicity

Univariable analysis		
	Odds Ratio	95% Confidence Interval
Guideline-recommended vancomycin dosing	0.85	0.41–1.78
Weight of 100kg or greater	2.57	1.15–5.76
Age greater than 65 years	1.71	0.83–3.51
Pitt Bacteremia Score of 4 or greater	2.62	1.29–5.31
Vancomycin trough concentration greater than 15 mg/dl	1.83	0.85–3.94
Concomitant nephrotoxins (aminoglycosides, intravenous contrast, vasopressors)	2.19	1.04–4.59
Vancomycin duration greater than 15 days	3.39	1.65–6.95
Multivariable analysis		
	Odds Ratio	95% Confidence Interval
Guideline-recommended vancomycin dosing	1.24	0.47–3.26
Pitt Bacteremia Score of 4 or greater	3.12	1.34–7.30
Concomitant nephrotoxins (aminoglycosides, intravenous contrast, vasopressors)	1.76	0.71–4.35
Weight of 100kg or greater	2.86	1.03–7.95
Vancomycin trough concentration greater than 15 mg/dl	2.07	0.82–5.22
Age greater than 65 years	2.60	1.04–6.46
Vancomycin duration greater than 15 days	3.48	1.48–8.21

Table 3

Univariable and multivariable analysis of risk factors for mortality

Univariable analysis		
	Odds Ratio	95% Confidence Interval
Guideline-recommended vancomycin dosing	0.70	0.32–1.58
Pitt Bacteremia Score of 4 or greater	1.80	0.86–3.78
Concomittant nephrotoxins (aminoglycosides, intravenous contrast, vasopressors)	1.38	0.64–2.97
Weight of 100kg or greater	1.53	0.66–3.56
Age greater than 65 years	2.91	1.36–6.27
Vancomycin trough concentration greater than 15 mg/dl	2.03	0.91–4.56
Development of nephrotoxicity	3.59	1.67–7.74
Multivariable analysis		
	Odds Ratio	95% Confidence Interval
Guideline-recommended vancomycin dosing	0.54	0.22–1.36
Development of nephrotoxicity	2.87	1.21–6.78
Pitt Bacteremia Score of 4 or greater	2.94	1.05–8.22
Age greater than 65 years	2.50	1.03–6.07