Risk Factors for Vancomycin Nephrotoxicity: Still a Matter of Debate*

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Vancomycin is considered the drug of choice to treat infections caused by methicillin-resistant *Staphylococcus aureus* (1). Nephrotoxicity is a dreaded adverse effect of vancomycin use, but its prevalence, risk factors, and prognostic importance are still a matter of debate. Current guidelines recommend higher target vancomycin through levels (15–20 µg/mL) (1, 2) to overcome bacterial resistance and to assure treatment response. Consequently, higher vancomycin doses have been used, potentially increasing nephrotoxicity risk (3, 4).

In this issue of *Critical Care Medicine*, Hanrahan et al (5) retrospectively assessed several risk factors for vancomycin nephrotoxicity (VN) in a cohort of critically ill patients. The prevalence of vancomycin-associated acute kidney injury (AKI) was 21%. The independent risk factors identified for VN using logistic regression analysis (LR) were longer therapy, simultaneous use of vasoactive drugs, higher trough serum concentrations, and intermittent infusion (InI).

A strength of this study was its number of patients (n = 1,430), which was greater than in most previous surveys (4, 6). There was a 35% loss of patients due to missing data. Age, weight, and estimated glomerular filtration rate (eGFR) of the excluded and included patients were similar, minimizing potential selection bias.

This timely article raises important aspects for consideration by future studies, especially those related to methodological aspects. The authors used the Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE) definition for AKI diagnosis, which considers changes in serum creatinine (SCr) and/or eGFR (7). Although newer AKI definitions, such as Acute Kidney Disease Network (AKIN) (8) and Kidney Disease Improving Global Outcomes (KDIGO) (9), have been proposed, the RIFLE criteria have been validated in several surveys assessing AKI in a variety of situations, generally using the SCr criteria (10). However, the formulas for eGFR have not been validated for AKI diagnosis, and the decreases in eGFR do not correspond to the increases in SCr in the RIFLE definition (11). The use of the RIFLE eGFR criterion might have overestimated the AKI prevalence in the present study. Additionally, the 24-hour period for the SCr measurements used for AKI diagnosis might be insufficient to differentiate VN from other transitory unrecorded renal insults, confounding AKI prevalence.

There is no universally accepted definition of acute VN; instead, 50% increases in SCr or absolute increases greater than 0.5 mg/dL are used most frequently (4, 6, 12). The heterogeneity of the AKI definitions reported to assess VN has been a drawback to the comparison of different studies. RIFLE and AKIN definitions have been infrequently used, and no study has included the KDIGO definition (13).

The most important risk factor for VN identified in the current study was InI, which is still a controversial point in the assessment of VN. It has been reported that continuous vancomycin infusion (CoI) achieves faster and more consistent therapeutic serum concentrations, reducing the development of antibiotic resistance (14). Some observational and retrospective studies have found that CoI is associated with less nephrotoxicity (12), whereas others have shown inconclusive results (15). Two randomized controlled trials (RCTs) assessed a small number of patients (16, 17), and the current guidelines for vancomycin therapy do not recommend the use of a CoI regimen (1, 2), considering the insufficient evidence supporting a definitive conclusion. An important limitation of the present study is that the infusion strategy groups were dissimilar, with more severely ill patients in the CoI group. This group showed higher Sequential Organ Failure Assessment scores, greater use of vasoactive drugs, and higher mortality. Those patients received a higher vancomycin dose, had a longer treatment period, disclosed a higher serum concentration level, and had a higher AKI prevalence on the bivariate analysis. The authors justify the increased odds ratio for nephrotoxicity found by LR in the InI group by the intersections between

*See also p. 2527.

Key Words: acute kidney injury; intensive care unit; risk factors; vancomycin

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vancomycin concentration and infusion methods (higher odds of nephrotoxicity for a certain vancomycin level in CoI group). However, it is not possible to exclude an overlap between InI and CoI groups that might have influenced this result. An alternative for overcoming this drawback would be the use of propensity score statistic methods.

A higher trough serum vancomycin concentration was detected as an independent risk factor for VN, as reported previously (3, 4). Nevertheless, because 90% of vancomycin is excreted by renal filtration, increased vancomycin levels can be either the cause or consequence of decreased glomerular filtration rate. To be sure about a true temporal relationship between elevated vancomycin serum levels and the development of nephrotoxicity, serial consecutive assessments of both SCr and vancomycin levels are needed. A prospective RCT would be able to overcome the methodological limitations cited above.

This study also highlights additional aspects to be improved in future surveys. Any simultaneous use of drugs associated with VN (aminoglycoside, amphotericin, piperacillin-tazobactam, contrast media, nonsteroidal anti-inflammatory drugs, calcineurin blockers, angiotensin-converting enzyme inhibitors, and furosemide) as well as the duration of their exposure must be recorded (6). Other variables that might influence VN must be studied. They should include simultaneous kidney insults (hypotension, surgeries, clinical events as stroke, myocardial infarction, pulmonary embolism, and septic shock), illness severity variables (vasoactive drugs dose, mechanical ventilation use, and lactate levels), and patient comorbidities, especially chronic kidney disease (CKD), a well-known risk factor for nephrotoxic AKI (18). Accurate assessments of the baseline renal function, incorporating updated formulas to evaluate eGFR, are of the utmost relevance. The impact of VN on early and long-term mortality and incident CKD will provide clinically relevant data.

The lack of a control group of similarly ill patients treated with antibiotics other than vancomycin jeopardizes the real estimation of VN; this limitation is shared by the current study and by most of the previously published surveys.

Most of the evidence related to the risk factors for VN is supported by observational studies and a few RCTs with small numbers of patients; thus, no data can be considered conclusive. Multicentric RCT studies with adequate sample sizes to assess the method of infusion that incorporate updated AKI definitions, standardized methods for vancomycin concentration measurement, and the sequential evaluation of both trough vancomycin and SCr levels are necessary. Identifying the risk factors for VN is a key step in the refinement of our capacity to stratify risk and to plan interventions to avoid this serious complication.

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Vancomycin-Associated Nephrotoxicity in the Critically Ill: A Retrospective Multivariate Regression Analysis*

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Objectives: To evaluate the influence of vancomycin dose, serum trough concentration, and dosing strategy on the evolution of acute kidney injury in critically ill patients.

Design: Retrospective, single-center, observational study.

Setting: University Hospital ICU, Birmingham, UK.

Patients: All critically ill patients receiving vancomycin from December 1, 2004, to August 31, 2009.

Intervention: None.

Measurements and Main Results: The prevalence of new onset nephrotoxicity was reported using Risk, Injury, Failure, Loss, End-stage renal disease criteria, and independent factors predictive of nephrotoxicity were identified using logistic regression analysis. Complete data were available for 1,430 patients. Concomitant vasoactive therapy (odds ratio = 1.633; $p < 0.001$), median serum vancomycin (odds ratio = 1.112; $p < 0.001$), and duration of therapy (odds ratio = 1.041; $p \leq 0.001$) were significant positive predictors of nephrotoxicity. Intermittent infusion was associated with a significantly greater risk of nephrotoxicity than continuous infusion (odds ratio = 8.204; $p \leq 0.001$).

Conclusions: In a large dataset, higher serum vancomycin concentrations and greater duration of therapy are independently associated with increased odds of nephrotoxicity. Furthermore, continuous infusion is associated with a decreased likelihood of nephrotoxicity compared with intermittent infusion. This large dataset supports the use of continuous infusion of vancomycin in critically ill patients. (*Crit Care Med* 2014; 42:2527–2536)

Key Words: acute kidney injury; glycopeptide; infection; intensive care unit; sepsis; vancomycin

***See also p. 2635.**

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is associated with significant morbidity and mortality in the ICU. MRSA is responsible for 10% of all infections (1) and 14% of all instances of sepsis (2). Furthermore, MRSA is associated with a 50% greater likelihood of mortality than methicillin-susceptible *Staphylococcus aureus* (3). Given that between 19% and 25% of patients colonized with MRSA develop infection, with an overall mortality rate as high as 6.3 per 100,000 infections (4), effective antibiotic treatment is critical to treatment success.

Vancomycin is the antibiotic most widely used for the treatment of infections mediated by MRSA (5). Of concern, MRSA with reduced susceptibility to vancomycin is increasing in prevalence with studies suggesting trough serum concentrations less than 10 mg/L are associated with the emergence of vancomycin-resistant *S. aureus* (6, 7). Subsequently, clinical practice guidelines now advocate targeting trough serum concentrations of 15–20 mg/L, which is much higher than the previous target of 5–10 mg/L (8–10). This increase in the target exposure is considered to increase the likelihood of concentration-related adverse effects, including nephrotoxicity.

Some authors have proposed that doses more than 4 g/d, high serum trough concentrations, and an increased duration of vancomycin therapy are associated with nephrotoxicity (1, 11, 12). To date, however, there is a relative paucity of large-scale data able to measure the significance of vancomycin exposure as an independent risk factor for nephrotoxicity.

This study aimed to evaluate the influence of vancomycin dose, serum trough concentration, and dosing strategy on the evolution of acute kidney injury in critically ill patients.

MATERIALS AND METHODS

A retrospective cohort study was conducted on data from the University Hospital Birmingham, a tertiary referral and university-affiliated hospital. This ICU treats up to 80 critically ill patients at any one time and manages approximately 4,500 patients annually. The ICU provides local and tertiary care for all adult specialties, including heart, lung, liver, kidney, and bone marrow transplantation. The data of all patients who received IV vancomycin from December 1, 2004, to August 31, 2009, were extracted from a central database. The data of patients receiving vancomycin by non-IV routes were not included in the primary database.

Local protocol dictated that patients with a central venous catheter receive vancomycin by continuous infusion. No criteria were established as to which patients should receive vancomycin by intermittent infusion, but typically, this would occur if 1) the clinician was not compliant with the protocol or 2) no central catheter was present. Data of those patients by which the dosing method was unknown or those patients who received vancomycin by both continuous and intermittent infusion were included in interests of maximizing available data. If a patient was the recipient of an intermittent infusion, serum concentrations were measured within 30 minutes of the next dose. If the patient was on continuous infusion, the samples were taken randomly, but at least 18 hours after the preceding dose change.

The study was approved by the South Birmingham Research Ethics Committee (09/H1207/140). Data extracted from the hospital's electronic database included sex, weight (where available), date of birth, ethnicity, hospital and ICU admission dates, ICU and hospital discharge dates, hospital discharge status, time of vancomycin prescription, administration start times, rate of infusion, dosage, serum creatinine concentration at admission, serum creatinine concentration during vancomycin therapy, trough serum vancomycin concentration, and MRSA status. If multiple trough serum vancomycin concentrations were available, the median and maximum measured concentrations were recorded.

As rifampicin's pulmonary penetration is often considered superior to vancomycin (13), any concomitant prescription was included in the analysis to measure effects it may have on clinical outcome. Furthermore, given reports of rifampicin renal toxicity (14, 15), inclusion allowed analysis of its influence on renal function when prescribed simultaneously with vancomycin. Given patients included in the analysis were admitted to the ICU, inotrope data were collected to account for potential confounding effects on renal function. Sequential Organ Failure Assessment (SOFA) (3, 16) data were also collected at the start of treatment. With the exception of Glasgow Coma Scale (GCS) and blood pressure, all components (ventilation status, worst daily Po_2/Fio_2 ratio, highest inotrope use, liver function, platelet count, and creatinine concentrations) of the SOFA score were calculated using data collected from the same electronic database.

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula (4, 17) for all serum creatinine concentrations obtained throughout the ICU stay. The primary endpoint, new onset nephrotoxicity, was defined as an increase in serum creatinine concentration more than or equal to 50%, a decrease in eGFR more than or equal to 25%, or a serum creatinine concentration more than or equal to 350 μmol/L (in the setting of an acute increase ≥ 44 μmol/L) as per the RIFLE acute kidney injury classification system (18). Secondary endpoints were death within 72 hours of the last recorded vancomycin dose (irrespective of treatment modality), all-cause mortality, and a combined endpoint of either death within 72 hours of vancomycin administration or nephrotoxicity.

The prevalence of new onset nephrotoxicity was reported, and univariate analysis was performed to determine data distribution and the prevalence of missing data. Data for which no serum vancomycin concentration, dosing amount, or creatinine concentration were available (n = 755) or which had incomplete SOFA score availability (n = 356) were excluded from analysis. Furthermore, where unique patients had multiple ICU admissions during the study period (n = 151), only data from the first episode were used. Continuous variables with a normal distribution are reported as mean ± SD and nonnormal variables are reported as median and interquartile range. The Pearson product-moment correlation coefficient was used to identify highly correlated potential predictive variables ($r > 0.8$) with the variable most predictive of nephrotoxicity included in further analysis. Predictive variables associated with the primary and secondary endpoints were explored using logistic regression analysis. Manual and backward stepwise techniques were used to identify the model with best fit. Interactions between predictive variables were included where multivariate and bivariate findings differed and inclusion of the interaction improved goodness-of-fit. Independent predictive variables with a p value of less than 0.05 were considered statistically significant. Goodness-of-fit was assessed by the Hosmer and Lemeshow statistic and the Nagelkerke R^2 index. Receiver operating characteristic (ROC) curves were used to explore thresholds for nephrotoxicity at different highest measured and median serum vancomycin concentrations. Youden index was used to identify the optimal threshold for maximizing sensitivity and specificity at specific threshold values. Statistical analysis was performed in SPSS (Version 20.0; IBM, Armonk, NY).

RESULTS

During the study period, 2,359 patients were prescribed vancomycin therapy in line with the study inclusion criteria. Of these, 2,208 were primary admissions, of which 1,430 had complete datasets (65%). Univariate analysis comparing

TABLE 1. Comparison of Baseline Characteristics Between Patients Included and Excluded From the Final Analysis

Variable	Excluded *n* = 778 (35%)	Included *n* = 1,430 (65%)	*p*
Age at admission	57.95	56.48	0.055
Day 1 modification of diet in renal disease	72.22	71.01	0.319
Weight	77.46	76.78	0.349

excluded and included patients showed no significant differences between age at admission ($p = 0.055$), day 1 MDRD ($p = 0.319$), or weight ($p = 0.349$) (**Table 1**). Median age was 60.0 years (45–70 yr) with 65% men (935/1,430). Median weight was 75.0 kg (67.0–86.0 kg). Vasoactive therapy was used in 62% of patients (885/1,430), whereas 6% of patients (92/1,430) received simultaneous rifampicin therapy. Furthermore, 11% of patients (150/1,430) were identified as MRSA positive. The median trough serum vancomycin concentration was 15.3 mg/L (9.6–19.6 mg/L), whereas the median length of vancomycin therapy was 4.4 days (2.3–8.6 d). The median average dose was 1.7 g (1.1–2.1 g) of vancomycin per day. The predominant method of administration was continuous infusion (46% or 653/1,430), followed by intermittent infusion (28% or 390/1,430); 16% of patients (221/1,430) received vancomycin by both continuous and intermittent infusion, whereas the mode of administration was not described in 11% of patients (150/1,430). The median SOFA score (not inclusive of GCS) was 6.0 (4.0–8.0). The prevalence of nephrotoxicity in the study population during ICU admission was 21% (300/1,430); ICU mortality for the study population was 20% (288/1,430). Patient demographics are summarized in **Table 2**. **Table 3** summarizes differences in clinical and demographic variables between patients who did and did not develop nephrotoxicity during ICU admission.

Patients who received vancomycin by intermittent infusion received a significantly lower median average daily dose (1.5 g [0.9–2.2 g]) than those who received vancomycin by continuous infusion (1.7 g [1.2–2.1 g]; $p = 0.003$), mixed method administration (1.7 g [1.2–2.1 g]; $p = 0.020$), or unknown method of administration (2.0 g [1.0–2.1 g]; $p = 0.005$). Furthermore, patients who received vancomycin by intermittent infusion (8.8 mg/L [6.5–11.2 mg/L]) had a significantly lower median serum vancomycin concentration than those who received it by continuous infusion (18.4 mg/L [15.6–21.2 mg/L]; $p \leq 0.001$). **Table 4** summarizes group differences by method of vancomycin administration.

ROC analysis indicated that the threshold for development of nephrotoxicity for median vancomycin concentration was 17.8 mg/L (sensitivity = 0.60, specificity = 0.71, Youden index = 0.31, area under the curve [AUC] = 0.677), whereas the threshold for highest measured serum vancomycin concentration during admission was 23.7 mg/L (sensitivity = 0.65, specificity = 0.74, Youden index = 0.39, AUC = 0.727). **Table 5** summarizes the risk of nephrotoxicity, sensitivity, and specificity for incremental increases in trough serum vancomycin concentration.

TABLE 2. Demographic Data of Patients Included in Final Analysis

Factors	*n* (%)
Sex (male)	935 (65)
Age, median (IQR)	60.0 (45–70)
Weight, median (IQR)	75.0 (67.0–86.0)
Sequential Organ Failure Assessment[a] score, median (IQR)	6.0 (4.0–8.0)
Median serum vancomycin concentration (mg/L), median (IQR)	15.3 (9.6–19.6)
Average vancomycin dose daily (g), median (IQR)	1.7 (1.1–2.1)
Length of vancomycin therapy (d), median (IQR)	4.4 (2.3–8.6)
ICU mortality	288 (20)
Nephrotoxicity	300 (21)
Death within 72 hr of last vancomycin	224 (16)
Nephrotoxicity or died within 72 hr of cessation	469 (32)
Infusion type	
Continuous infusion	653 (46)
Intermittent dosing	390 (28)
Mixed dosing	221 (16)
Unknown	166 (12)
Simultaneous vasoactive therapy	885 (62)
Methicillin-resistant *Staphylococcus aureus* positive	150 (11)
Simultaneous rifampicin therapy	92 (6)

IQR = interquartile range.

[a]Glasgow Coma Scale (GCS) values were not available for inclusion; thus, Sequential Organ Failure Assessment (SOFA) total is SOFA minus GCS.

Predictors of Nephrotoxicity

The most parsimonious logistic regression model identified duration of therapy in days (odds ratio [OR] = 1.041; $p < 0.001$), simultaneous vasoactive therapy (OR = 1.633; $p < 0.001$), and median trough serum vancomycin concentration (OR = 1.112; $p < 0.001$) as independent positive predictors of nephrotoxicity (**Table 6**). Intermittent infusion was associated with a significantly greater risk of nephrotoxicity than continuous infusion (OR = 8.204; $p < 0.001$). There was, however, a significant interaction between median serum vancomycin concentration and infusion method. A 1 mg/L increase in the median serum vancomycin concentration

TABLE 3. Summary of Nephrotoxic and Nonnephrotoxic Groups

Variable	Nephrotoxicity ($n = 300$) Median (IQR)	Nonnephrotoxic ($n = 1,130$) Median (IQR)	p
Age (yr)	62.0 (51.0–71.0)	59.0 (44.0–70.0)	0.004[a]
Sex (male)	191 (63.7%)	744 (65.8%)	0.482
Weight (kg)	75.0 (66.0–85.0)	75.0 (67.0–85.7)	0.366[a]
Sequential Organ Failure Assessment score[b]	7.0 (5.0–9.0)	6.0 (4.0–8.0)	< 0.001[a]
Median vancomycin serum concentration (mg/L)	18.9 (13.8–22.2)	14.2 (9.2–18.4)	< 0.001[a]
Duration of treatment (d)	8.0 (4.0–15.8)	4.0 (2.0–6.9)	< 0.001[a]
Average vancomycin daily (g/d)	1.1 (0.6–1.6)	1.8 (1.3–2.3)	< 0.001[a]
Total vancomycin exposure (g)	8.1 (4.8–13.9)	6.8 (4.0–11.0)	< 0.001[a]
Infusion method			
Continuous	161 (53.7%)	492 (43.5%)	0.001
Intermittent	77 (25.7%)	313 (27.7%)	0.001
Mixed	44 (14.7%)	177 (15.7%)	0.001
Unknown	18 (6.0%)	148 (13.1%)	0.001
Simultaneous rifampicin	23 (7.7%)	69 (6.1%)	0.327
Methicillin-resistant *Staphylococcus aureus*	38 (12.7%)	112 (9.9%)	0.166
Simultaneous vasoactive prescription	234 (78.0%)	651 (57.6%)	< 0.001

IQR = interquartile range.
[a]Calculated by Mann-Whitney *U* statistic as variables fail Kolmogorov-Smirnov normality testing.
[b]Glasgow Coma Scale (GCS) values were not available for inclusion; thus, Sequential Organ Failure Assessment (SOFA) total is SOFA minus GCS.

had lower odds of nephrotoxicity in the intermittent infusion group compared with the continuous infusion group (OR = 0.92; $p = 0.013$). There was adequate goodness-of-fit (Hosmer and Lemeshow test $X^2 = 13.31$, $df = 8$, $p = 0.102$; Nagelkerke $R^2 = 0.192$).

Predictors of Nephrotoxicity or Death Within 72 Hours (Combined Endpoint)

Independent positive predictors of nephrotoxicity or death within 72 hours of vancomycin treatment are as follows (Table 6): SOFA (OR = 1.128; $p < 0.001$), positive MRSA status (OR = 1.696; $p = 0.008$), simultaneous vasoactive therapy (OR = 1.501; $p = 0.008$), median vancomycin serum concentration (OR = 1.094; $p \leq 0.001$), and duration of therapy (OR = 1.032; $p \leq 0.001$). There was a significantly greater odds of nephrotoxicity or death within 72 hours of dosing in those who received vancomycin by intermittent infusion compared with continuous infusion (OR = 1.645; $p = 0.007$). Goodness-of-fit was adequate (Hosmer and Lemeshow test $X^2 = 14.553$, $df = 8$, $p = 0.068$; Nagelkerke $R^2 = 0.208$).

Predictors of Death Within 72 Hours

Independent predictors of death within 72 hours of the last vancomycin dose showed SOFA (OR = 1.190; $p < 0.001$), simultaneous rifampicin therapy (OR = 2.075; $p = 0.010$), and median trough serum vancomycin (OR = 1.034; $p = 0.009$) as positive predictors (**Table 7**). The odds of death from mixed method dosing (OR = 0.619; $p = 0.047$) was less than that for patients receiving continuous infusion; intermittent infusion was nonsignificantly different to continuous infusion (OR = 0.726; $p = 0.167$). Goodness-of-fit was adequate (Hosmer and Lemeshow test $X^2 = 5.469$, $df = 8$, $p = 0.706$; Nagelkerke $R^2 = 0.113$).

Predictors of All-Cause Mortality

SOFA (OR = 1.172; $p < 0.001$), simultaneous rifampicin therapy (OR = 1.793; $p = 0.031$), median trough serum vancomycin (OR = 1.038; $p = 0.001$), and duration of vancomycin therapy (OR = 1.015; $p = 0.001$) were significant positive predictors of all-cause mortality (Table 7). Weight was nonsignificantly negatively predictive of mortality (OR = 0.992; $p = 0.081$). Intermittent infusion (OR = 0.735; $p = 0.141$) and mixed method dosing (OR = 0.554; $p = 0.008$) had lower odds of death than participants receiving vancomycin by continuous infusion. There was adequate goodness-of-fit (Hosmer and Lemeshow test $X^2 = 7.560$, $df = 8$, $p = 0.478$; Nagelkerke $R^2 = 0.139$).

DISCUSSION

There are few large-scale studies examining the influence of vancomycin therapy on nephrotoxicity in critically ill patients. The need to better understand the vancomycin exposure-toxicity

TABLE 4. Summary of Patients Data Receiving Vancomycin by Infusion Method Type

Percent (%)	Continuous Infusion ($n = 653$)	Intermittent Infusion ($n = 390$)	Mixed ($n = 221$)	Unknown ($n = 166$)	p^a
Sex, male (%)	417 (63.9)	260 (66.7)	145 (65.6)	113 (68.1)	0.685
Age, median (IQR)	59 (44–69)	61 (47.8–71)	59 (45–70)	63 (46.8–72)	0.060
Weight, median (IQR)	75 (66.1–85)	75 (67.8–88)	75 (65–84.5)	75 (65–87.9)	0.331
Sequential Organ Failure Assessment score, median (IQR)	7.0 (5.0–9.0)	5.0 (3.0–7.0)	6.0 (3.0–8.0)	6.0 (4.0–8.0)	< 0.001
Median serum vancomycin concentration (mg/L), median (IQR)	18.4 (15.6–21.2)	8.8 (6.5–11.2)	15.5 (12.1–19.1)	11.9 (8.2–17.7)	< 0.001
Average vancomycin dose daily (g), median (IQR)	1.7 (1.2–2.1)	1.5 (0.9–2.2)	1.7 (1.2–2.1)	2.0 (1.0–2.1)	0.003
Length of vancomycin therapy (d), median (IQR)	5.3 (3.4–10.3)	4.4 (2.5–7.3)	5.0 (2.9–9.2)	0.8 (0.4–1.2)	< 0.001
ICU mortality (%)	172 (26.3)	49 (12.6)	31 (14.0)	36 (21.7)	< 0.001
Nephrotoxicity (%)	161 (24.7)	77 (19.7)	44 (19.9)	18 (10.8)	0.001
Death within 72 hr of last vancomycin (%)	130 (19.9)	36 (9.2)	25 (11.3)	33 (19.9)	< 0.001
Nephrotoxicity or died within 72 hr of cessation (%)	253 (38.7)	101 (25.9)	66 (29.9)	49 (29.5)	< 0.001
Simultaneous vasoactive therapy (%)	469 (71.8)	177 (45.4)	151 (68.3)	88 (53.0)	< 0.001
Methicillin-resistant *Staphylococcus aureus* positive (%)	64 (9.8)	56 (14.4)	20 (9.0)	10 (6.0)	0.014
Simultaneous rifampicin therapy (%)	35 (5.4)	38 (9.7)	14 (6.3)	5 (3.0)	0.009
Highest measured serum vancomycin concentration (mg/L), median (IQR)	24.7 (18.7–28.5)	11.8 (8.4–17.2)	19.9 (15.8–26.0)	12.7 (9.0–19.1)	< 0.001
Cumulative vancomycin dose (g), median (IQR)	9.0 (6.0–14.4)	5.8 (4.0–9.0)	8.0 (4.7–13.8)	2.0 (1.5–3.0)	< 0.001

IQR = interquartile range.

[a]Calculated by Kruskall-Wallis statistic where linear variable as variables fail Kolmogorov-Smirnov normality testing.

TABLE 5. Precision of Predicting Nephrotoxicity and Incremental Risk Increase of Different Threshold Values for Highest Measured Vancomycin Serum Concentrations

Threshold Level (mg/L)	Nephrotoxicity (%)	Relative Risk Increase[a]	Sensitivity	Specificity	Youden Index	Positive Predictive Value	Negative Predictive Value
10	21.7%		1	0.043	0.043	0.217	1
15	23.2%	1.069	0.936	0.178	0.115	0.232	0.914
20	26.2%	1.207	0.84	0.372	0.212	0.262	0.898
25	33.1%	1.525	0.747	0.600	0.346	0.331	0.899
30	41.5%	1.912	0.603	0.774	0.377	0.415	0.880
> 30	47.9%	2.207	0.303	0.912	0.216	0.478	0.831

[a]Relative to first threshold level (10 mg/L).

TABLE 6. Logistic Regression Analysis With Nephrotoxicity and Nephrotoxicity Odds Ratio Death Endpoints

	Nephrotoxicity		
	All Factors		Final Model
Factors	OR (95% CI)	*p*	OR (95% CI)
Age[b]	1.032 (0.957–1.114)	0.413	–
Weight	0.998 (0.990–1.007)	0.708	–
Sex[c]	0.900 (0.679–1.193)	0.464	–
Sequential Organ Failure Assessment score[d]	1.044 (0.997–1.092)	0.065	–
Infusion method[e]			
Intermittent	1.022 (0.625–1.671)	0.932	8.204 (2.875–23.411)
Mixed	2.139 (1.251–3.657)	0.005	2.781 (0.661–11.705)
Unknown	1.267 (0.732–2.194)	0.398	8.050 (2.403–26.967)
Simultaneous rifampicin prescription	1.029 (0.602–1.757)	0.918	–
Methicillin-resistant *Staphylococcus aureus* positive	0.865 (0.564–1.326)	0.505	–
Simultaneous vasoactive prescription	0.683 (0.496–0.940)	0.019	1.633 (1.226–2.174)
Median serum vancomycin (mg/L)	1.104 (1.077–1.132)	< 0.001	1.112 (1.085–1.139)
Median serum vancomycin × intermittent	–	–	0.924 (0.868–0.983)
Median serum vancomycin × mixed	–	–	0.961 (0.889–1.039)
Median serum vancomycin × unknown	–	–	0.891 (0.838–0.947)
Duration of therapy (d)	1.040 (1.027–1.053)	< 0.001	1.041 (1.028–1.054)
Goodness-of-fit			
Hosmer and Lemeshow test	$X^2 = 10.666$, $df = 8$	0.221	$X^2 = 13.307$, $df = 8$
Nagelkerke R^2	0.184		0.192

OR = odds ratio.

[a]Death during vancomycin dosing or within 72 hr of cessation.

[b]Age was re-categorized as an ordinal scale in 10-year increments: odds > 1 is the increase in odds of the outcome within a 10-year increase in the factor.

[c]OR compares female relative to male.

[d]Glasgow Coma Scale (GCS) values were not available for inclusion; thus, Sequential Organ Failure Assessment (SOFA) total is SOFA minus GCS.

[e]OR is relative to continuous infusion.

Dashes indicate there was no variable output in the indicated model.

relationship is important, given recent guidelines advocating higher serum trough concentrations to counter the decreasing susceptibility of MRSA (9, 10). In this study of 1,430 critically ill patients, we found that elevated median trough serum vancomycin concentration is associated with a significant increase in risk of nephrotoxicity with each 1 mg/L increase in concentration associated with a 11.2% increase in the odds of nephrotoxicity. Duration of therapy was also positively predictive of nephrotoxicity with every 1-day increase in the duration of therapy being associated with a 4.1% increase in the odds of nephrotoxicity.

These findings are in concordance with other studies that show duration of vancomycin therapy to have a significant positive association with nephrotoxicity (12, 19, 20). Of interest, Pritchard et al (11) noted a significant rising trend in vancomycin serum concentrations ($p < 0.001$) without an increase in the prevalence of nephrotoxicity during the same period. This finding, however, may be confounded by the association of increasing serum trough concentrations with a decreasing duration of therapy during the same period. We hypothesize that if organisms with reduced susceptibility to vancomycin continue to become more prevalent, then the potential combination of increased duration of treatment and higher trough serum concentrations may result in a further increased prevalence of nephrotoxicity.

We found that continuous infusion was significantly less likely to cause nephrotoxicity in multivariate analysis than all other infusion types despite patients on continuous infusion receiving greater daily doses than those receiving intermittent infusion of vancomycin. Patients who received intermittent infusion had an 8.2 times higher odds of nephrotoxicity than those who received continuous infusion, and this effect

Nephrotoxicity OR Death[a]				
All Factors			Final Model	
p	OR (95% CI)	*p*	OR (95% CI)	*p*
–	1.072 (0.996–1.153)	1.031	–	–
–	1.000 (0.992–1.008)	0.725	–	–
–	1.148 (0.878–1.502)	0.411	–	–
–	1.134 (1.085–1.185)	< 0.001	1.128 (1.080–1.179)	< 0.001
< 0.001	1.525 (1.059–2.195)	0.308	1.645 (1.149–2.356)	0.007
0.163	0.924 (0.645–1.325)	0.504	0.945 (0.660–1.352)	0.755
0.001	1.431 (0.935–2.191)	0.356	1.487 (0.973 – 2.274)	0.067
–	1.305 (0.788–2.162)	0.604	–	–
–	1.644 (1.096–2.466)	0.066	1.696 (1.145–2.511)	0.008
< 0.001	1.445 (1.066–1.957)	0.003	1.501 (1.111–2.029)	0.008
< 0.001	1.088 (1.063–1.114)	< 0.001	1.094 (1.069–1.120)	< 0.001
0.013	–	–	–	–
0.314	–	–	–	–
< 0.001	–	–	–	–
< 0.001	1.031 (1.019–1.043)	0.187	1.032 (1.020–1.044)	< 0.001
0.102	$X^2 = 21.489$, $df = 8$ 0.212	0.006	$X^2 = 14.553$, $df = 8$ 0.208	0.068

was independent of baseline renal function and serum vancomycin concentration. This confirms the conclusion reached in a recent meta-analysis that suggested continuous infusion is associated with a significantly reduced risk of nephrotoxicity compared with intermittent infusion (relative risk = 0.6; 95% CI, 0.4–0.9; $p = 0.02$) (21). Furthermore, mixed and unknown dosing strategies were associated with lower odds of nephrotoxicity than intermittent infusion. This is expected, due to the fact that the latter categories likely consist of a large proportion of patients dosed by continuous infusion in accordance with unit protocol. Furthermore, it has been shown that up to 66% of patients receiving intermittent infusion do not reach target concentrations compared with 30% of patients who receive continuous infusion (22). Given the rise in trough concentration recommendations over the study period (10), the intermittent infusion group may have simply been undertreated.

The higher prevalence of nephrotoxicity in the continuous infusion group compared with the intermittent infusion group (24.7% vs 19.7%) in bivariate analysis deserves mention as this suggests the possibility of confounding. As described above, the median serum vancomycin concentration was significantly higher in patients receiving continuous infusion, and this was identified as the main factor hypothesized to be responsible for this confounding effect (Table 4). In addition, there was a significant interaction between median serum vancomycin concentration and infusion method in multivariate analysis, such that an increase in median serum concentration was associated with a higher odds of nephrotoxicity in those who received vancomycin by continuous infusion compared with those with intermittent infusion. As discussed previously, 66% of patients receiving intermittent infusion do not reach target concentrations. Therefore, it could very well be that a shift to the right in

TABLE 7. Logistic Regression Analysis With Death Within 72 Hours of Vancomycin Dosing and All-Cause Mortality as Endpoints

	Death Within 72 Hr of Vancomycin Dosing		
	All Factors		Final Model
Factors	OR (95% CI)	*p*	OR (95% CI)
Age[b]	1.047 (0.957–1.145)	0.318	–
Weight	0.997 (0.987–1.006)	0.495	–
Sex[c]	1.203 (0.867–1.670)	0.269	–
Sequential Organ Failure Assessment score[d]	1.189 (1.126–1.255)	< 0.001	1.190 (1.133–1.249)
Infusion method[e]			
Intermittent	0.699 (0.438–1.116)	0.134	0.726 (0.461–1.143)
Mixed	0.620 (0.386–0.997)	0.049	0.619 (0.386–0.994)
Unknown	1.443 (0.906–2.296)	0.122	1.379 (0.878–2.164)
Simultaneous rifampicin	1.816 (1.009–3.266)	0.047	2.075 (1.190–3.619)
Methicillin-resistant *Staphylococcus aureus* positive	1.370 (0.834–2.251)	0.214	–
Simultaneous vasoactive prescription	1.045 (0.707–1.543)	0.826	–
Median serum vancomycin (mg/L)	1.030 (1.002–1.058)	0.032	1.034 (1.008–1.060)
Duration of vancomycin therapy (d)	1.006 (0.997–1.015)	0.215	–
Nephrotoxicity	0.932 (0.644–1.350)	0.709	–
Goodness-of-fit			
Hosmer and Lemeshow test	$X^2 = 2.969$, $df = 8$	0.936	$X^2 = 5.469$, $df = 8$
Nagelkerke R^2	0.120		0.113

OR = odds ratio.

[a]Death during ICU admission.

[b]Age was re-categorized as an ordinal scale in 10-year increments: odds > 1 is the increase in odds of the outcome within a 10-year increase in the factor.

[c]OR compares female relative to male.

[d]Glasgow Coma Scale (GCS) values were not available for inclusion; thus, Sequential Organ Failure Assessment (SOFA) total is SOFA minus GCS.

[e]OR is relative to continuous infusion.

the serum concentration curve is increasing the influence that median serum trough concentration has on nephrotoxicity in the continuous infusion group. Again, AUC would be ideal to study this relationship.

To our knowledge, this is the first large-scale study that has shown vancomycin administration by continuous infusion is associated with decreased nephrotoxicity. Unfortunately, the decrease in acute kidney injury associated with continuous infusion does not translate to improved mortality. Intermittent infusion was associated with a nonsignificant lower odds of mortality than continuous infusion ($p = 0.141$). A greater percentage of the cohort received continuous infusion (Table 2), and the duration of treatment and median SOFA score were both higher in the continuous infusion group (Table 4), alluding to potential nonmeasured factors confounding the result. Given local protocol dictates that prescription of vancomycin by continuous infusion can only be administered by central catheter, and inherently, a patient requiring central access is likely to have greater morbidity, continuous infusion being more predictive of mortality than intermittent infusion in this cohort is not surprising. A large prospective study is required to categorically determine the effect of treatment method on mortality.

In addition to being associated with nephrotoxicity, duration of vancomycin therapy also appears positively predictive of all-cause mortality. We are, however, unable to speculate on why this is the case as information on the indication for vancomycin therapy, infection site, and sensitivities of the targeted organism are unknown. These factors may all contribute to extended vancomycin regimens in the context of greater morbidity. It is interesting to note that although nephrotoxicity was positively associated with mortality in the enter model, it was not included in the final logistic regression model due to poor significance. We hypothesize that follow-up at 28 days, or latter, would identify this trend as significant.

The analysis included in this study provided interesting results. In phase 1 of their study, Pritchard et al (11) showed that a median trough vancomycin serum concentration of

All-Cause Mortality[a]				
All Factors			Final Model	
p	OR (95% CI)	*p*	OR (95% CI)	*p*
–	1.069 (0.984–1.161)	0.116	–	–
–	0.994 (0.985–1.003)	0.186	0.992 (0.984–1.001)	0.081
–	1.197 (0.884–1.619)	0.245		–
< 0.001	1.166 (1.110–1.226)	0.000	1.172 (1.121–1.226)	< 0.001
0.167	0.682 (0.447–1.040)	0.076	0.735 (0.488–1.107)	0.141
0.047	0.545 (0.353–0.884)	0.006	0.554 (0.358–0.855)	0.008
0.163	1.219 (0.781–1.903)	0.384	1.218 (0.784–1.892)	0.380
0.010	1.650 (0.952–2.859)	0.074	1.793 (1.055–3.046)	0.031
–	1.373 (0.868–2.171)	0.176	–	–
–	1.134 (0.795–1.618)	0.488	–	–
0.009	1.030 (1.005–1.056)	0.020	1.038 (1.014–1.063)	0.002
–	1.014 (1.005–1.023)	0.003	1.015 (1.006–1.024)	0.001
–	1.199 (0.863–1.668)	0.279	–	–
0.706	$X^2 = 10.586$, $df = 8$	0.226	$X^2 = 7.560$, $df = 8$	0.478
	0.146		0.139	

14 mg/L was the threshold for development of nephrotoxicity. Here, we have shown that maximum sensitivity and specificity for nephrotoxicity occurred at a median concentration of 17.8 mg/L. Though not a large increase in concentration compared to Pritchard et al (11), our study suggests that the lower spectra of recommended serum concentrations are relatively safe. In clinical practice, the median concentration is not prospectively useful. We found the threshold for nephrotoxicity is 23.7 mg/L when considering the highest measured serum concentration observed for a single patient. A prudent clinician, with the aid of therapeutic drug monitoring (TDM), thus has the potential to negate significant risk of nephrotoxicity by ensuring measured concentrations do not surpass these values. Furthermore, it is clear that greater concentrations do have an association with nephrotoxicity (Table 5), and this must be considered when targeting high serum concentrations to circumvent the challenge of a high minimum inhibitory concentration (MIC). As MRSA MICs continue to rise, it will be necessary to look to other agents for therapeutic purposes, particularly if the clinical context deems the risk of acute kidney injury not tolerable to the patient.

It must be recognized that this study is limited by its retrospective nature, and as such, causality cannot be demonstrated. An inherent flaw of retrospective data analysis is the difficulty to account for all potential confounding variables and simultaneous treatment agents. A prospective randomized controlled trial is necessary to confirm these results. Although we are able to explore factors associated with nephrotoxicity in patients receiving vancomycin, we are unable to quantify the overall risk of nephrotoxicity associated with vancomycin use in a general ICU population. We also acknowledge that SOFA has not been validated for tracking the severity of illness in ICU. Despite this, inclusion of this SOFA score allowed for the degree of morbidity to be partially accounted for in the multivariate analysis. Furthermore, the titration of vancomycin dosing based on MDRD determinations of eGFR is not validated and may not be optimal. Finally, generalizability to other ICU

population groups needs to be ensured by validation with an independent dataset.

In summary, we have shown that trough serum vancomycin concentrations and duration of therapy are associated with increased risk of nephrotoxicity. Further, baseline organ function (SOFA) and simultaneous vasoactive therapy are predictive of nephrotoxicity. Given recommendations to increase serum vancomycin concentrations to 15–20 mg/L to combat rising MICs, this information reinforces the valuable role that TDM plays in optimizing safe vancomycin therapy. We have also demonstrated that continuous infusion is associated with significantly less nephrotoxicity than dosing by intermittent infusion. Despite this, there is still a lack of data showing whether the method of administration impacts on all-cause mortality and resolution of infection, despite our results showing a small nonsignificant trend toward survival advantage in the intermittent infusion cohort. Given that continuous infusion is associated with decreased nephrotoxicity, reaches target concentrations faster with fewer samples (when loading doses are used) (23, 24), has less variability in the daily infused dose, reduces costs (25), and has less variability in serum concentrations (26), this large dataset supports the use of continuous infusion of vancomycin in critically ill patients.

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