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CLINICAL THERAPEUTICS

A Quasi-Experiment To Study the Impact of Vancomycin Area under the Concentration-Time Curve-Guided Dosing on Vancomycin-Associated Nephrotoxicity

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ABSTRACT Evidence suggests that maintenance of vancomycin trough concentrations at between 15 and 20 mg/liter, as currently recommended, is frequently unnecessary to achieve the daily area under the concentration-time curve (AUC_{24}) target of ≥400 mg · h/liter. Many patients with trough concentrations in this range have AUC_{24} values in excess of the therapeutic threshold and within the exposure range associated with nephrotoxicity. On the basis of this, the Detroit Medical Center switched from trough concentration-guided dosing to AUC-guided dosing to minimize potentially unnecessary vancomycin exposure. The primary objective of this analysis was to assess the impact of this intervention on vancomycin-associated nephrotoxicity in a single-center, retrospective quasi-experiment of hospitalized adult patients receiving intravenous vancomycin from 2014 to 2015. The primary analysis compared the incidence of nephrotoxicity between patients monitored by assessment of the AUC_{24} and those monitored by assessment of the trough concentration. Multivariable logistic and Cox proportional hazards regression examined the independent association between the monitoring strategy and nephrotoxicity. Secondary analysis compared vancomycin exposures (total daily dose, AUC, and trough concentrations) between monitoring strategies. Overall, 1,280 patients were included in the analysis. After adjusting for severity of illness, comorbidity, duration of vancomycin therapy, and concomitant receipt of nephrotoxins, AUC-guided dosing was independently associated with lower nephrotoxicity by both logistic regression (odds ratio, 0.52; 95% confidence interval [CI], 0.34 to 0.80; $P = 0.003$) and Cox proportional hazards regression (hazard ratio, 0.53; 95% CI, 0.35 to 0.78; $P = 0.002$). AUC-guided dosing was associated with lower total daily vancomycin doses, AUC values, and trough concentrations. Vancomycin AUC-guided dosing was associated with reduced nephrotoxicity, which appeared to be a result of reduced vancomycin exposure.

KEYWORDS therapeutic drug monitoring, pharmacokinetics, pharmacodynamics, trough concentration, acute kidney injury

Despite the widespread clinical use of vancomycin, the optimal strategy for monitoring vancomycin therapy has not been elucidated (1). The consensus guidelines for monitoring vancomycin therapy published by the American Society of Health-System Pharmacists (ASHP) in collaboration with the Infectious Diseases Society of American and the Society of Infectious Diseases (IDSA) Pharmacists (SIDP) in 2009

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recommend a target of vancomycin trough (minimum) concentrations (C_{min}) of 15 to 20 mg/liter for complicated infections, such as bacteremia, endocarditis, osteomyelitis, and pneumonia (2). Trough concentrations are used in practice as a more simplistic surrogate for the true pharmacokinetic parameter predictive of vancomycin activity against *Staphylococcus aureus*, the daily area under the concentration-time curve (AUC_{24}). Trough concentrations between 15 and 20 mg/liter are recommended to maximize the likelihood of achieving AUC_{24} values of ≥400 mg · h/liter. In turn, this ensures an AUC_{24}-to-MIC ratio of ≥400 for organisms with MICs of ≤1 mg/liter (2).

Although maintenance of trough concentrations between 15 and 20 mg/liter may ensure that a majority of patients achieve AUC_{24} values of ≥400 mg · h/liter, recent pharmacokinetic data suggest that more than half of patients can meet this AUC_{24} target with trough concentrations of <15 mg/liter (3). This may explain why many studies evaluating vancomycin exposure-response relationships demonstrate that AUC_{24} thresholds are associated with improved outcomes in patients with serious methicillin-resistant *Staphylococcus aureus* infections, while data demonstrating the same effect with trough concentrations of >15 mg/liter are generally lacking (1, 4–8). In contrast, targeting of trough concentrations 15 to 20 mg/liter can impart an increased risk of vancomycin-associated nephrotoxicity. The association between vancomycin therapy and nephrotoxicity has been well described in the literature (9–14). Vancomycin trough concentrations of >15 mg/liter have consistently been associated with increased nephrotoxicity (9, 10, 14, 15). Proposed AUC_{24} thresholds for nephrotoxicity vary widely, but it is likely that a higher proportion of patients with trough concentrations of >15 mg/liter have AUC_{24} values within the range associated with nephrotoxicity (3, 10–12, 16, 17). Thus, targeting of trough concentrations of between 15 and 20 mg/liter may result in unnecessary drug exposure in some patients and a corresponding increased risk of nephrotoxicity in a large proportion of patients (3).

One potential solution to this issue is adoption of an approach to monitoring vancomycin therapy on the basis of a target AUC_{24} rather than a target serum trough concentration (18). This concept serves as the basis for administration and monitoring of vancomycin by continuous infusion (19). Despite the potential safety benefit associated with continuous infusion, debate regarding the true benefit and practicality issues with dedication of a line for administration for 24 h have left intermittent infusion as the predominant administration approach, particularly in the United States (20–22). However, clinical data to support an AUC-based monitoring approach with intermittent infusion are lacking. In 2015, due to clinician concerns regarding vancomycin-associated nephrotoxicity and the emerging body of evidence suggesting that targeting of trough concentrations between 15 and 20 mg/liter may lead to overexposure, the Detroit Medical Center (DMC) implemented an AUC-guided dosing strategy. The primary objective of this study was to compare the incidence of nephrotoxicity in patients receiving vancomycin monitored by use of the AUC with that in patients receiving vancomycin monitored by use of the trough concentration. The secondary objective of this analysis was to assess the impact of this novel dosing approach on vancomycin exposures, quantified by the total daily vancomycin dose, AUC, and trough concentration.

RESULTS

Description of cohort. There were 1,280 patients identified and included in the study: 546 patients in the trough concentration-monitoring period and 734 patients in the AUC-monitoring period. The majority of patients were male (55.5%), and the mean age was 59.1 years (standard deviation [SD], 16.9 years). The median Elixhauser comorbidity index and the acute physiology and chronic health evaluation II (APACHE II) score were 5 (interquartile range [IQR], 3 to 7) and 13 (IQR, 8 to 20), respectively. Common comorbidities included hypertension (73.5%), chronic pulmonary disease (40.8%), diabetes (39.3%), heart failure (31.3%), renal disease (17.1%), and obesity (15.0%). The most common indications for vancomycin therapy were lower respiratory tract infection (44.3%), sepsis of unknown source (13.8%), bacteremia (12.9%), and bone/joint infec-

tion (11.8%). Eight hundred patients (62.5%) received at least 1 concomitant nephrotoxic medication, with the most common ones being furosemide (38.8%), angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) (31.7%), and intravenous (i.v.) contrast dye (10.9%). Nephrotoxicity, defined by the vancomycin consensus guidelines, was observed in 8.4% of patients, while both Akin stage 1 or worse and a Rifle category of risk or worse were observed in 18.6% of patients.

Comparison of patient characteristics and nephrotoxicity outcomes between AUC- and trough concentration-guided dosing groups. The demographics and clinical characteristics of patients in the AUC- and trough concentration-guided dosing groups are displayed in Table 1. Although the demographics were similar between groups, the Elixhauser comorbidity indexes and APACHE II scores were significantly higher in the AUC-guided dosing group than in the trough concentration-guided dosing group and a larger proportion of patients in the AUC-guided dosing group than the trough concentration-guided dosing group received at least 1 concomitant nephrotoxin (64.9 versus 59.4%; $P = 0.048$). The indications for vancomycin were generally similar between the two groups; however, the patients in the AUC-guided dosing group were more likely than the patients in the trough concentration-guided dosing group to have a pneumonia indication (50.3% versus 36.3%; $P < 0.001$).

There were no statistically significant differences in nephrotoxicity, determined by bivariate analysis, between the two cohorts by any of the three definitions used (Table 1). However, after accounting for severity, comorbidity, and the receipt of concomitant nephrotoxins in multivariable regression analysis (Table 2), AUC-guided dosing was associated with less frequent nephrotoxicity, as defined by the vancomycin dosing guidelines (adjusted odds ratio [aOR], 0.514; 95% confidence interval [CI], 0.332 to 0.794; $P = 0.003$), while the receipt of concomitant furosemide (aOR, 1.771; 95% CI, 1.127 to 2.784; $P = 0.013$), the Elixhauser comorbidity index (aOR, 1.149; 95% CI, 1.060 to 1.245; $P = 0.001$), the duration of vancomycin therapy (aOR, 1.093; 95% CI, 1.044 to 1.145; $P < 0.001$), and the APACHE II score (aOR, 1.070; 95% CI, 1.045 to 1.097; $P < 0.001$) were independent predictors of nephrotoxicity. Similar results were seen in the Cox proportional hazards regression, where AUC-guided dosing was associated with less frequent nephrotoxicity (Fig. 1). AUC-guided dosing was also associated with less frequent nephrotoxicity when multivariable logistic regression modeling was performed using Akin stage 2 or worse (aOR, 0.564; 95% CI, 0.380 to 0.838; $P = 0.005$) and a Rifle category of injury or worse (aOR, 0.611; 95% CI, 0.375 to 0.995; $P = 0.048$) as the definition for nephrotoxicity. However, no association between AUC-guided dosing and Akin stage 1 or 3 or the risk or failure Rifle category was observed (data not shown). These results are consistent with those of the *post hoc* matched analyses, where AUC-guided dosing was associated with reduced toxicity by the 2009 guideline, Akin stage 2, and the Rifle category of risk toxicity definitions (see Tables S1 and S2 in the supplemental material).

Comparison of vancomycin exposures between AUC- and trough concentration-guided dosing groups. Vancomycin exposures were higher in patients receiving trough concentration-guided dosing than AUC-guided dosing (Tables 1 and 3). Patients monitored by use of the trough concentration had higher total daily vancomycin dosages than patients monitored by use of the AUC from 0 to 24 h (3,250 mg [IQR, 2,500 to 4,250 mg] versus 3,000 mg [IQR, 2,000 to 3,750 mg]; $P < 0.001$), 24 to 48 h (5,250 mg [IQR, 4,000 to 7,500 mg] versus 5,000 mg [IQR, 3,750 to 6,500 mg]; $P < 0.001$), and 48 to 72 h (7,500 mg [IQR, 5,500 to 10,250 mg] versus 7,000 mg [IQR, 5,000 to 9,250 mg]; $P = 0.001$). Measured trough concentrations were significantly higher in the trough-guided dosing group than in the AUC-guided dosing group (15.0 mg/liter [IQR, 10.8 to 19.5 mg/liter] versus 12.0 mg/liter [IQR, 8.4 to 15.7 mg/liter]) ($P < 0.001$). The median calculated AUC_{24} for the AUC-guided dosing group was 471.5 mg · h/liter (IQR, 361.5 to 576.7 mg · h/liter). Table 3 displays the results of Bayesian estimated vancomycin exposure profile subgroup analysis. Vancomycin exposure by AUC and C_{min} was significantly higher in the trough-guided dosing group. This held true at both time points at which the trough concentration was analyzed (at 24 h [$C_{min}24$] and at 48 h

TABLE 1 Bivariate comparisons of patient characteristics and outcomes between groups monitored by use of the trough concentration and AUC

Variable	Values for the following groups:		*P* value
	Trough concn-guided dosing (*n* = 546)	AUC-guided dosing (*n* = 734)	
Mean ± SD age (yr)	59.1 ± 17.5	59.0 ± 16.5	0.964
No. (%) male patients	296 (54.2)	414 (56.4)	0.435
Median (IQR) wt (kg)	67.9 (56.5–75.1)	66 (56.5–75.1)	0.758
Median (IQR) baseline SCr (mg/dl)	0.9 (0.7–1.1)	0.9 (0.7–1.2)	0.056
Median (IQR) baseline CL_{CR} (ml/min)	80.1 (56.6–114.9)	78.3 (54.2–111.3)	0.257
Median (IQR) APACHE II score	12 (7–17)	14 (9–22)	<0.001
Median (IQR) Elixhauser comorbidity index	5 (3–6)	5 (3–7)	0.013
No. (%) of patients with the following comorbid conditions:			
Congestive heart failure	161 (29.5)	239 (32.6)	0.241
Cardiac arrhythmia	181 (33.2)	289 (39.4)	0.022
Valvular disease	66 (12.1)	66 (9.0)	0.072
Peripheral vascular disease	79 (14.5)	118 (16.1)	0.431
Neurological disorder	141 (25.8)	197 (26.8)	0.684
Chronic pulmonary disease	209 (38.3)	313 (42.6)	0.116
Diabetes mellitus, complicated	71 (13.0)	106 (14.4)	0.461
Liver disease	41 (7.5)	64 (8.7)	0.435
Peptic ulcer disease	19 (3.5)	9 (1.2)	0.006
HIV infection	10 (1.8)	8 (1.1)	0.265
Metastatic cancer	25 (4.6)	40 (5.4)	0.483
Solid tumor without metastasis	57 (10.4)	76 (10.4)	0.961
Obesity	85 (15.6)	107 (14.6)	0.624
No. (%) of patients receiving one or more of the following concomitant nephrotoxins:	324 (59.4)	476 (64.9)	0.048
i.v. contrast dye	46 (8.4)	93 (12.7)	0.016
Furosemide	187 (34.4)	309 (42.1)	0.004
ACEi/ARB	182 (33.3)	219 (29.8)	0.182
Aminoglycoside	33 (6.0)	52 (7.1)	0.460
Median (IQR) no. of concomitant nephrotoxins	1 (0–1)	1 (0–1)	0.042
No. (%) of patients with the following indication for vancomycin:			
Pneumonia	198 (36.3)	369 (50.3)	<0.001
Bacteremia	77 (14.1)	88 (12.0)	0.264
Sepsis of unknown source	70 (12.8)	107 (14.6)	0.368
Bone/joint infection	68 (12.5)	83 (11.3)	0.529
Endovascular infection	11 (2.0)	4 (0.5)	0.016
Diabetic foot infection	20 (3.7)	14 (1.9)	0.053
Intra-abdominal infection	16 (2.9)	19 (2.6)	0.711
Other	86 (15.8)	50 (6.8)	<0.001
Vancomycin exposure			
Median (IQR) cumulative vancomycin dose (mg)			
0–24 h	3,250 (2,438–4,250)	3,000 (2,000–3,750)	<0.001
0–48 h	5,250 (4,000–7,500)	5,000 (3,750–6,500)	<0.001
0–72 h	7,500 (5,438–10,250)	7,000 (5,000–9,250)	0.001
Median (IQR) duration of vancomycin therapy (days)	5.6 (4.1–7.3)	5.3 (4.0–7.1)	0.076
Median (IQR) measured trough concn (mg/liter)	15.0 (10.8–19.5)	12.0 (8.4–15.7)	<0.001
Median (IQR) calculated AUC_{24} (mg · h/liter)	Not calculated	471.5 (361.5–576.7)	
No. (%) of patients with the following nephrotoxicity outcomes:			
2009 vancomycin consensus guideline definition	54 (9.9)	54 (5.4)	0.107
Akin stage			
1 or worse	106 (19.4)	132 (18.0)	0.515
2 or worse	64 (11.7)	65 (8.9)	0.092
3	17 (3.1)	22 (3.0)	0.905
Rifle category			
Risk or worse	99 (18.1)	139 (18.9)	0.714
Injury or worse	38 (7.0)	43 (5.9)	0.423
Failure	17 (3.1)	22 (3.0)	0.905

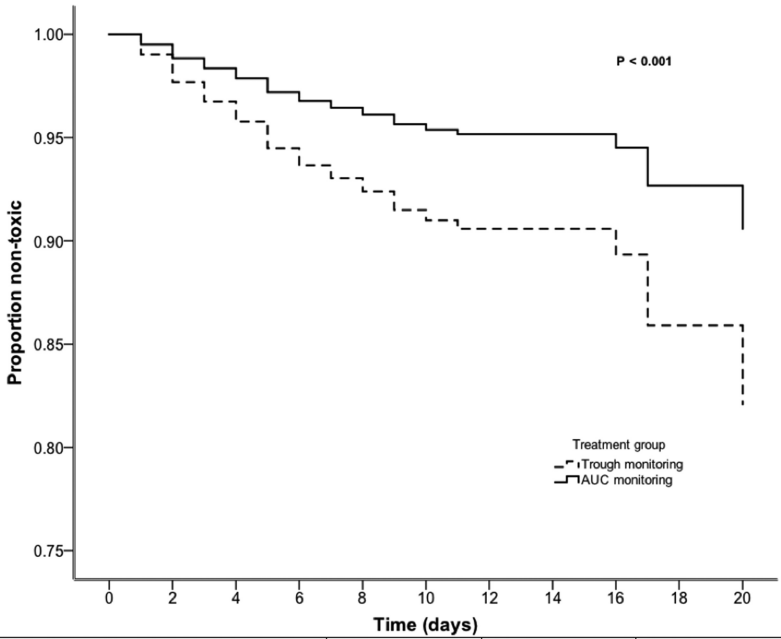
TABLE 2 Multivariable logistic regression for 2009 vancomycin consensus guideline-defined nephrotoxicity

Variable	Unadjusted OR	95% CI for unadjusted OR	Adjusted OR	95% CI for adjusted OR	*P* value
AUC monitoring	0.724	0.488–1.074	0.514	0.332–0.794	0.003
Concomitant furosemide	3.226	2.136–4.873	1.771	1.127–2.784	0.013
Elixhauser comorbidity index	1.274	1.186–1.368	1.149	1.060–1.245	0.001
Duration of therapy	1.124	1.074–1.175	1.093	1.044–1.145	<0.001
APACHE II score	1.084	1.061–1.106	1.070	1.045–1.097	<0.001
Concomitant i.v. contrast dye	2.406	1.538–3.765			
Concomitant tobramycin	1.195	0.880–4.165			

[C_{min}48]) and at both time points at which the AUC was analyzed (from time zero to 24 h [AUC_{0-24}] and from 24 h to 48 h [AUC_{24-48}]).

DISCUSSION

After controlling for the clinical differences between the two groups, AUC-guided dosing was independently associated with less nephrotoxicity than trough concentration-guided dosing. This was seen in both the multivariable logistic and Cox proportional regression models while controlling for other independent predictors of nephrotoxicity and the matched analyses. Many of these factors were more common in the AUC-guided dosing group and may explain why no difference in nephrotoxicity between the two groups was observed in the bivariate analysis. The stark difference in the severity of illness between the two groups was likely introduced by the exclusion of patients receiving concomitant piperacillin-tazobactam. Most critically ill patients requiring broad-spectrum empirical antibiotics during the trough concentration-guided dosing period would have received piperacillin-tazobactam and been excluded, as this was the institutional antipseudomonal agent of choice during the time of the study. However,



Variable	Hazard Ratio	95% CI	*P* value
AUC-TD	0.501	0.336 – 0.748	0.001
Concomitant furosemide	1.636	1.072 – 2.496	0.022
Elixhauser Comorbidity Index	1.123	1.044 – 1.208	0.002
APACHE II score	1.066	1.042 – 1.091	<0.001
Concomitant IV contrast	1.508	0.972 – 2.339	0.067
Concomitant tobramycin [a]	-	-	-
Duration of therapy, days [a]	-	-	-

[a] Not retained in final model

FIG 1 Time to nephrotoxicity by Cox proportional hazards regression. AUC-TD, AUC- and trough concentration-guided dosing.

TABLE 3 Bayesian estimated vancomycin exposure profile subgroup analysis

Variable	Values for the following groups[a]:		*P* value
	Trough concn-guided dosing group (n = 150)	AUC-guided dosing group (n = 150)	
C_{min24} (mg/liter)	12.7 (8.9–16.6)	10.0 (5.7–13.4)	<0.001
C_{min48} (mg/liter)	14.2 (10.3–19.5)	12.5 (8.3–16.7)	0.003
AUC_{0-24} (mg · h/liter)	705 (540–883)	474 (360–611)	<0.001
AUC_{24-48} (mg · h/liter)	663 (538–857)	532 (406–667)	<0.001

[a]Data represent the median (IQR).

due to a piperacillin-tazobactam shortage and institutional data associating it with vancomycin-associated nephrotoxicity, during the AUC-guided dosing period most critically ill patients would have received cefepime and been included in the analysis (23). This is supported by the disproportionate number of patients in the AUC-guided dosing group with a pneumonia indication. These patients would likely have been deemed candidates for empirical antipseudomonal therapy. Thus, by excluding patients receiving concomitant piperacillin-tazobactam, more critically ill patients were included in the AUC-guided dosing group.

The rationale behind AUC-guided vancomycin dosing was to reduce the rates of nephrotoxicity by decreasing overall vancomycin exposure while maintaining AUC_{24} values in the therapeutic range. This notion is supported by the literature linking excess vancomycin exposure to nephrotoxicity and is consistent with the rationale for the administration of vancomycin by continuous infusion (9, 10, 14, 15, 17, 19, 24). Coupled with recent data demonstrating that therapeutic vancomycin AUC_{24} values can be achieved in many patients with trough concentrations of <15 mg/liter, we hypothesized that implementation of AUC-guided dosing would reduce vancomycin exposure and, in turn, vancomycin-associated nephrotoxicity. In addition to reduced nephrotoxicity, we observed decreased vancomycin exposure in the AUC-guided dosing group by multiple measures of drug exposure. Trough concentration and AUC measures were approximately 20% lower in the patients with AUC-guided dosing. This translated to fewer patients in the AUC-guided dosing group with trough concentrations of >15 mg/liter. Published AUC_{24} thresholds for nephrotoxicity vary, but most are ≥600 mg · h/liter (10–12, 16). In the Bayesian subgroup analysis, the median AUC_{0-24} and AUC_{24-28} for the trough-guided dosing group were both ≥600 mg · h/liter. In contrast, the median AUC_{0-24} and AUC_{24-28} and calculated AUC_{24} for the AUC-guided dosing group were all <600 mg · h/liter. Thus, it appears that patients in the AUC-guided dosing group were less likely to have vancomycin exposure profiles in the range associated with nephrotoxicity. Despite this reduction in vancomycin exposure, the median (IQR) AUC_{0-24} and AUC_{24-28} and the calculated AUC_{24} for the AUC-guided dosing group indicate that most patients still had AUC_{24} values in excess of the current therapeutic target of 400 mg · h/liter for staphylococci with an MIC of ≤1 mg/liter. This analysis was not designed to examine the impact of AUC-guided dosing on efficacy, but these data suggest that this monitoring approach can reduce overall vancomycin exposure while maintaining exposure profiles within the therapeutic range.

This study has multiple limitations that warrant mention. First, it was a retrospective study conducted at a single health care system in Detroit, MI. Although missing data are frequently an issue with retrospective analyses, the nephrotoxicity outcomes were based on objective definitions using the serum creatinine concentration (SCr), which was readily available for all included patients. It is also important to note that institution-specific practices and exclusion criteria, such as the exclusion of patients receiving concomitant piperacillin-tazobactam, may limit the generalizability of these findings. Excluding these patients was necessary considering that this important variable would have been disproportionately represented in the trough concentration monitoring period, thus imparting substantial bias against trough concentration-guided therapy. Some patients with indications for vancomycin therapy were also

excluded, as the current DMC vancomycin monitoring guidelines did not recommend AUC_{24} targets for their indications. In particular, skin and soft tissue infections are a common indication for vancomycin, and it is important to note that these data may not be applicable to that population. Finally, this analysis evaluated the impact of AUC-guided vancomycin dosing only on toxicity and was not designed to examine the potential impact on efficacy. The indications for therapy were based on the initial order from the prescriber, and many patients likely did not have a true infection. Although the AUC measures indicate that the vancomycin concentrations in most patients in the AUC-guided dosing group were in the therapeutic range, we cannot be sure what impact the transition to AUC-guided dosing may have had on the ultimate infection-related outcome.

In conclusion, AUC-guided vancomycin dosing was associated with significantly reduced nephrotoxicity compared to that associated with trough concentration-guided dosing. When evaluated via multivariable logistic regression, AUC-guided dosing was associated with an approximately 50% reduced odds of nephrotoxicity. This was potentially a result of the reduced vancomycin exposure in the AUC-guided dosing group, as measured by the total daily dose, AUC, and trough concentration, while the efficacy target of an AUC_{24} of $\geq$400 mg · h/liter was maintained when the MIC was $\leq$1 mg/liter. Although this vancomycin dosing approach shows promise in reducing vancomycin-associated nephrotoxicity, additional study is required to examine the impact on its clinical efficacy against invasive *Staphylococcus aureus* infections.

MATERIALS AND METHODS

Study design and population. This was a retrospective, quasi-experimental study including hospitalized patients receiving intravenous vancomycin at four adult hospitals within DMC. Both the Wayne State University Institutional Review Board and the DMC Research Review Committee approved the study. All patients who received vancomycin for at least 72 h for a documented or suspected infection from January 2014 through December 2015 were eligible for inclusion. In 2014, vancomycin was dosed to target trough concentrations of between 15 and 20 mg/liter in patients with disease states for which it was indicated. In January 2015, the vancomycin dosing guidelines for the treatment of invasive infections were revised to target an AUC_{24} of 400 to 600 mg · h/liter. Details related to vancomycin dosing during each time period are described below. At least one vancomycin trough concentration obtained near steady state and within the first 96 h of therapy was required for inclusion in the trough concentration-guided dosing group. For inclusion in the AUC-guided dosing group, a minimum of two vancomycin concentrations in samples drawn during the same dosing interval within the first 96 h of therapy were required. Patients with a preexisting need for renal replacement therapy (RRT) or a baseline serum creatinine concentration (SCr) of $\geq$2 mg/dl were excluded. Patients who received vancomycin to treat meningitis, skin and soft tissue infections without concomitant bacteremia, urinary tract infections, or surgical prophylaxis were excluded, as the current DMC vancomycin monitoring guidelines do not recommend AUC_{24} targets for these indications. Due to the emerging body of evidence correlating use of the combination of vancomycin and piperacillin-tazobactam with increased nephrotoxicity and a piperacillin-tazobactam shortage, piperacillin-tazobactam use sharply declined during the study period (23, 25, 26). To account for this potential confounding variable, patients receiving concomitant piperacillin-tazobactam were excluded.

Patient data. Patient clinical data, including demographics, comorbidities, medication administration records, laboratory values, physiologic parameters, and indication for vancomycin therapy, were obtained from the electronic medical record by querying the organization's business intelligence software. Comorbid conditions were defined using the codes from the *International Classification of Disease*, 9th revision (ICD-9), and the *International Classification of Disease*, 10th revision, *Clinical Modification* (ICD-10-CM). The degree of patient comorbidity was quantified using the Elixhauser comorbidity index (27). The severity of illness was quantified using the acute physiology and chronic health evaluation II (APACHE II) score and the worst physiological parameters within 24 h of vancomycin initiation (28). The indication for vancomycin therapy was obtained from the electronic antibiotic indication field completed by the prescriber at the time of initial order entry. The dates and times of administration of vancomycin and other potentially nephrotoxic medications were identified from the electronic record of barcoded medication administration. The following medications or medication classes were considered potential nephrotoxins: aminoglycosides, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), amphotericin B, calcineurin inhibitors, intravenous contrast dye, loop diuretics, polymyxins, and vasopressors. Renal function was assessed by determination of the serum creatinine concentration (SCr) and creatinine clearance (CL_{CR}), which was estimated by use of the Cockcroft-Gault formula (29).

Vancomycin dosing at the Detroit Medical Center. Prior to 2015, vancomycin was dosed to target serum vancomycin trough concentrations of 15 to 20 mg/liter on the basis of basic pharmacokinetic principles and published pharmacokinetic equations for vancomycin (30, 31). Trough concentrations were measured near steady state (i.e., after 3 to 5 doses), and the dose and frequency were adjusted as

TABLE 4 Nephrotoxicity outcome definitions[a]

Outcome	Definition
2009 vancomycin consensus guideline	SCr increase of ≥0.5 mg/dl and ≥50% the baseline SCr for ≥2 consecutive measurements
Akin stage	
1	SCr increase of ≥0.3 mg/dl or ≥1.5 times baseline SCr
2	SCr increase of ≥0.5 mg/dl or ≥2 times baseline SCr
3	SCr increase of ≥3 times baseline SCr or acute increase of 0.5 mg/dl if SCr is ≥4 mg/dl
Rifle category	
Risk	SCr increase of ≥1.5 times baseline SCr or CL_{CR} decrease of >25%
Injury	SCr increase of ≥2 times baseline SCr or CL_{CR} decrease of >50%
Failure	SCr increase of ≥3 times baseline SCr or CL_{CR} decrease of >75%

[a]The baseline SCr was defined as the SCr value immediately preceding the first dose of vancomycin, if available. In cases in which SCr was determined after the first vancomycin dose, the first SCr value immediately after the initial vancomycin dose was considered the baseline SCr.

necessary. In January 2015, the institutional guidelines for vancomycin dosing for the treatment of invasive infections were revised to target an AUC_{24} of 400 to 600 mg · h/liter. The upper end of the AUC_{24} target range was selected on the basis of data suggesting an association between an AUC_{24} of >600 mg · h/liter and an increased risk of nephrotoxicity (11). In order to calculate patient-specific AUC_{24} values, two postinfusion serum vancomycin concentrations were measured. AUC_{24} was calculated by estimating the AUC during the infusion by use of the trapezoidal rule ($AUC_{inf} = C_{max} + C_{min}/2 \cdot$ time of infusion, where AUC_{inf} is the AUC from time zero to infinity and C_{max} is the maximum concentration) and the AUC during the elimination phase (AUC_{elim}) via the logarithmic trapezoidal rule ($AUC_{elim} = C_{max} - C_{min}$/elimination rate constant). The AUC for a given dose was then calculated by adding AUC_{inf} and AUC_{elim}. Finally, AUC_{24} was calculated by multiplying this number by the number of daily doses.

Outcomes. The primary outcome in this analysis was the comparative rate of acute kidney injury, assessed by three different definitions of vancomycin nephrotoxicity (Table 4). The baseline SCr was defined as the SCr immediately preceding the first dose of vancomycin, if available. In cases in which the sample in which SCr was determined was drawn after the first vancomycin dose, the first SCr immediately after the initial vancomycin dose was considered the baseline SCr. Secondary endpoints were measures of vancomycin exposure, including the total daily vancomycin dose, AUC, and trough concentration.

Data analysis. In the primary analysis, the independent association between the vancomycin dosing strategy and nephrotoxicity, as defined by the vancomycin consensus guidelines, was examined. Patients who developed acute kidney injury were first compared to those who did not in a bivariate analysis using the chi-square/Fisher exact test or the Student *t* test/Mann-Whitney U test as appropriate. Multivariable logistic regression analysis was then used to evaluate the independent predictors of nephrotoxicity. The variables associated with nephrotoxicity with biological plausibility in bivariate analysis ($P < 0.1$) were simultaneously entered into candidate regression models and removed individually using a backward elimination procedure until only variables with an adjusted *P* value of <0.1 remained. Vancomycin exposure variables (total daily dose, AUC, trough concentration) were not candidates for the regression analysis because they lie in the causal pathway between the monitoring strategy and nephrotoxicity. Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test; models with a nonsignificant result were considered adequate. The multicolinearity of candidate regression models was assessed by use of the variance inflation factor, with values of <3 considered acceptable. The association between the monitoring approach and the time to nephrotoxicity was also assessed via Cox proportional hazards regression, constructed in the same backward elimination approach as the logistic regression. Due to unanticipated differences in the severity of illness between the treatment groups, *post hoc* matched analyses were also performed with patients matched on APACHE II score ±3.

As a secondary analysis, the vancomycin exposures achieved with the two monitoring approaches were compared. First, the total daily vancomycin dose and clinically measured steady-state trough concentrations were compared between the two groups in the entire cohort. AUC_{24} values could not be directly calculated for the trough concentration-guided dosing period due to a lack of multiple serum vancomycin concentrations per dose interval. As such, it was not possible to directly compare the calculated AUC_{24} values for the entire cohort. In order to allow a comparison of AUC exposures between the two dosing strategies, a subgroup analysis was performed using a Bayesian estimation on 300 patients with a bacteremia or pneumonia indication. Patients with these indications from each group were first matched on indication and APACHE II score ±3. One hundred fifty pairs were then randomly selected for comparison. The concentration-time profiles for these patients were estimated via the maximum *a posteriori* probability (MAP) Bayesian function of the ADAPT V program using a previously published 2-compartment population pharmacokinetic model as the Bayesian prior (32, 33). This approach has been previously validated for estimation of the vancomycin AUC using trough-only serum concentration sampling (3). Day 1 and 2 AUC values (AUC_{0-24} and AUC_{24-48}, respectively) and day 1 and 2 trough concentrations ([C_{min}24] and [C_{min}48], respectively) were then compared between groups using the Mann-Whitney U test.

All statistical tests were two-sided, and *P* values of ≤0.05 were considered statistically significant. Statistical analyses were performed using SPSS (version 24.0) software (SPSS, Armonk, NY).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.01293-17.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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