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AN EVALUATION OF THE INCIDENCE OF NEPHROTOXICITY AFTER A LOADING DOSE OF VANCOMYCIN IN PATIENTS WITH SEVERE RENAL IMPAIRMENT

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☐ **Abstract—Background: Loading doses of vancomycin assist in the rapid achievement of target trough concentrations. Patients with renal dysfunction have been excluded from studies evaluating loading doses. Objective: The purpose of this study was to investigate nephrotoxicity related to initial vancomycin dose in patients with severe renal dysfunction. Methods: A retrospective cohort study was approved by the Institutional Review Board of a large, academic health system. Adults were included if they received intravenous vancomycin in the emergency department and presented with creatinine clearance < 30 mL/min. Chronic dialysis patients were excluded. The primary outcome was incidence of nephrotoxicity after an initial high (>20 mg/kg) vs. low (≤20 mg/kg) dose of vancomycin. Secondary outcomes included dialysis, vancomycin concentrations, length of stay, in-hospital mortality, and a composite outcome of nephrotoxicity or dialysis. Results: Of the 927 patients included in the analysis, nephrotoxicity occurred in 7.2% and 13.8% of patients in the high- and low-dose groups, respectively ($p < 0.01$). Patients in the high-dose group had a reduced risk of nephrotoxicity (relative risk 0.53; 95% confidence interval 0.35–0.78). The reduction in risk remained after fitting a generalized linear model adjusting for weight, age, sex, initial serum creatinine, diabetes, and chronic kidney disease (relative risk 0.61; 95% confidence interval 0.39–0.93). Limitations of this study include its retrospective design and single-center population. Conclusion: These data suggest that vancomycin loading doses do not increase nephrotoxicity compared with lower doses in patients with severe renal dysfunction. These patients should be included in future studies relating to vancomycin loading doses.**

☐ **Keywords—medication safety; infectious disease; nephrotoxicity; renal failure; vancomycin; antibiotics; sepsis**

This research was performed at Christiana Care Health System, Newark, Delaware.

INTRODUCTION

The time to reach therapeutic vancomycin concentrations can be reduced by administering loading doses. A loading dose is a 25–30-mg/kg initial dose prior to maintenance therapy and has been recommended for complicated infections by consensus guidelines to quickly attain target trough concentrations of 15–20 μg/mL (1). Patients resuscitated with large fluid boluses may exhibit volume changes and therefore necessitate loading doses (2). Although loading doses are recommended to optimize efficacy, nephrotoxicity is often questioned. A survey of clinical pharmacists showed that only 42% of institutions always administer vancomycin loading doses, and it is thought that this may be related to fears of toxicity (3). A retrospective cohort study of 597 patients studied vancomycin initial doses prior to and after implementation of an electronic order set in the emergency department (ED), which recommended a 20–30-mg/kg loading dose (4).

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Although there was a significant improvement in appropriate prescribing, the mean initial dose of vancomycin only increased from 14.6 mg/kg (SD 4.9) to 17.4 mg/kg (SD 5.7) ($p < 0.0001$). This study also evaluated a subset of critically ill patients and found that appropriate prescribing (defined as initial dose > 20 mg/kg, or > 15 mg/kg for urinary source) only increased from 28.4% to 44.7% ($p = 0.0441$) after order set implementation. Although electronic vancomycin dosing protocols are improving prescribing patterns, loading doses continue to be underutilized in the ED.

A prospective trial of vancomycin loading doses found that patients who received a 30-mg/kg initial dose had significantly higher trough concentrations at 12 h compared with a traditional 15-mg/kg dose; 37% of patients in the loading dose group attained a trough concentration of 15 μg/mL or higher at 12 h compared with 3% in the 15-mg/kg group (5). There was no significant difference in nephrotoxicity between a 30-mg/kg loading dose and nonloading doses of 15 mg/kg, with an incidence of 6.1% in the 15-mg/kg dose group and 4% in the loading dose group. These results are consistent with the 5–7% rate of nephrotoxicity reported for vancomycin monotherapy and suggests that loading doses may not increase nephrotoxicity risk (1). Although the previous study provides important safety data, patients with creatinine clearances (CrCl) below 50 mL/min were excluded, making generalizability to patients with diminished renal function questionable (5). Evidence on the efficacy and safety of vancomycin loading doses in renal impairment has been identified as a necessary topic for further research (6).

In the ED, time-sensitive therapies are initiated when current or baseline renal function may be unknown. Vancomycin loading doses may prompt concerns for supratherapeutic concentrations or further nephrotoxicity in patients with poor renal function. Due to the lack of data in this population, these patients may not be treated aggressively despite having severe infections. The objective of this study was to evaluate the safety of vancomycin loading doses administered to patients with CrCl < 30 mL/min upon presentation to the ED.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort study conducted in three EDs within a large academic health system. Patients who received intravenous vancomycin between May 1, 2013 and September 30, 2015 were included. This study period was selected based on the implementation of a clinical decision support tool recommending a 25–30-mg/kg loading dose of vancomycin to providers at the time of electronic order entry. This study was approved by the Institutional Review Board.

Patient Selection

Patients with CrCl < 30 mL/min who received a dose of intravenous vancomycin in the ED were included. CrCl was calculated using the Cockcroft-Gault formula. Ideal body weight was used in the formula unless the patient's actual weight was less than ideal body weight, in which case actual body weight was used. This was based on the hospital's vancomycin dosing by pharmacy protocol. The serum creatinine (SCr) used for this inclusion parameter was the first documented SCr after arrival. Although this did not distinguish patients with acute and chronic renal failure, a baseline SCr is often unavailable in the ED. Patients were included if they were age 18 years or older and subsequently admitted to the hospital from the ED. Exclusion criteria included: no documented weight or height during the hospital admission, < 2 SCr values after initial vancomycin dose, pregnancy, and chronic dialysis status as identified by International Classification of Diseases, Ninth Revision codes V45.11 (renal dialysis status) or 54.98 (peritoneal dialysis). Orders for hemodialysis between 2010 and study enrollment were utilized to identify patients whose chronic dialysis status required clarification through chart review. Patients with multiple admissions during the study period had only the most recent admission in the study period included.

Dosing Groups

The high-dose group was determined by an initial vancomycin dose > 20 mg/kg based on actual body weight. The comparator group (low dose) received an initial dose ≤ 20 mg/kg. Utilizing 20 mg/kg instead of 25 mg/kg ensured that all patients with a higher-than-standard dose were captured in the high-dose group as guidelines recommend 15–20 mg/kg as a traditional maintenance dose. Previous studies also have used this dosing breakpoint to evaluate loading doses, as weight is often estimated in the ED (7).

Outcome Measures

The primary outcome was the incidence of nephrotoxicity within 120 h from the initial dose of vancomycin. This was defined as two SCr values greater than the initial value by 0.5 mg/dL or 50% after the initial dose of vancomycin (1). A composite outcome of meeting nephrotoxicity criteria or dialysis order within the first 120 h after initial dose was also evaluated to capture patients that might not have met the SCr threshold for

nephrotoxicity due to reduction in SCr by dialysis. Secondary outcomes included length of stay (hospital and intensive care unit), in-hospital mortality, dialysis order within 120 h of initial vancomycin dose, and incidence of a supratherapeutic vancomycin concentration within 120 h of initial dose.

In this study, supratherapeutic concentrations were defined as > 25 μg/mL at a time of 20 h or greater after the previous dose. The institution's vancomycin dosing by pharmacy protocol can be ordered at the provider's discretion and is typically initiated after the initial dose is administered in the ED. The protocol recommends that patients with CrCl < 30 mL/min are not placed on a standing dose, rather, they are re-dosed with one-time doses before a random vancomycin concentration becomes subtherapeutic. The institution's dosing protocol recommends timing the first random vancomycin concentration 24 h following the previous dose for patients with CrCl < 30 mL/min, however, these concentrations may be drawn early for convenience. Concentrations drawn prior to that time would be expected to be falsely elevated, therefore, the value of > 25 μg/mL was selected to account for concentrations that may have been drawn early.

Concomitant use of nephrotoxic medications was also obtained. Administration of the following medications within 120 h of the first vancomycin dose were collected: tobramycin, amikacin, gentamicin, piperacillin-tazobactam, acyclovir, captopril, enalapril, enalaprilat, lisinopril, lisinopril/hydrochlorothiazide, losartan, valsartan, bumetanide, furosemide, ethacrynic acid, tacrolimus, cyclosporine, amphotericin B, and tenofovir.

Data Analysis

Data were evaluated using Stata® statistical software version 12.1 (8). Group differences in demographic and clinical characteristics were analyzed using *t*-tests for continuous variables and chi-square for categorical variables. All data were assessed for normality using the Shapiro-Wilk test. Differences for covariates that were nonnormally distributed were examined using the Wilcoxon Rank-Sum test, and Box-Cox transformations were conducted to normalize these variables prior to inclusion within the regression models. Generalized linear models utilizing a log-binomial regression model were fit to compute unadjusted and adjusted relative risks assessing the association between dosing and nephrotoxicity. Covariates were included within the adjusted model if there was a statistically significant difference found between groups.

Sample size calculations were based on assumptions of a two-tailed test with alpha (type 1 error rate) equal to 0.05 and a beta (type 2 error rate) of 0.20. This corresponds to a test with 80% power. As it was expected that there would be fewer patients in the high-dose group, the allocation ratio for calculating sample size was set at a rate of 4 to 1 comparing those in the low-dose and high-dose groups, respectively. To detect a 5.3% difference in the incidence of nephrotoxicity as seen in previous studies, it was predicted that a total sample size of 1428 patients would be needed, with 1142 in the low-dose group and 286 in the high-dose group (7). However, once the data were examined, it was discovered that the allocation ratio was closer to 1:1. With equal numbers of patients in the low-dose and high-dose groups, a post hoc power calculation revealed that the power of the study was 83%.

To determine the impact of the selection of a 20-mg/kg cutoff on the results, a sensitivity analysis was conducted utilizing a 25-mg/kg cutoff. Results from the two models were then compared to examine differences in the interpretation that may result from the definition of the high-dose group. Finally, two post hoc subgroup analyses were performed. The first examined the association between initial dose and nephrotoxicity separately for patients that received only one dose of vancomycin compared with those who continued therapy. The second analysis was completed only for those patients who received five or more doses of vancomycin.

RESULTS

Patients who received a vancomycin dose in the ED during the study period were evaluated for enrollment. A total of 927 patients were included for analysis of the primary outcome, with an equitable distribution between groups (Figure 1).

Baseline Characteristics

Overall, the mean age of the cohort was 75 years, with an average initial SCr of 2.76 mg/dL and CrCl of 19.9 mL/min. Patients in the high-dose group were slightly older, of lower weight, and there were more females than in the low-dose group (Table 1). Initial SCr concentrations

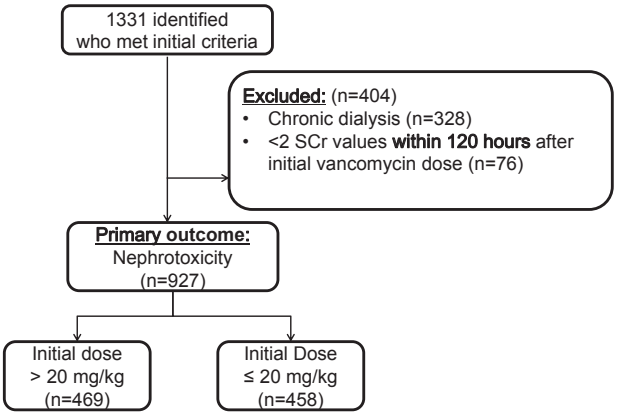

Figure 1. Enrollment diagram. SCr = serum creatinine.

were slightly higher in the low-dose group; however, there was no statistically significant difference in initial CrCl between the two groups. There were no differences in the number of patients who were continued on vancomycin therapy or the presence of concomitant nephrotoxic medications. The median initial dose for the low-dose group and the high-dose groups were 1250 mg (16.2 mg/kg) and 1750 mg (24.9 mg/kg), respectively. Vancomycin doses were generally capped at 2500 mg (37/927, 4%), with a brief period when 8 patients received doses up to 3000 mg before the institution changed its maximum dose. Additionally, the median number of total vancomycin doses during the hospital stay did not differ between groups, with two doses (interquartile range [IQR] 2) for each group. There were 521 patients (56.2%) dosed per pharmacist-driven protocol, and this did not differ between groups. For these patients only, goal vancomycin trough concentrations were available for data collection, with the majority targeting a goal of 15–20 μg/mL.

Primary Outcome

The primary outcome of nephrotoxicity occurred in 13.8% of patients in the low-dose group and 7.2% of patients in the high-dose group (Figure 2, $p < 0.01$). There was a 47% reduction in the risk of nephrotoxicity when high doses are compared with low (relative risk [RR] 0.53, 95% confidence interval [CI] 0.35–0.78). Adjusted models were then fit, including those factors that may have biased selection of initial dose (weight, age, sex, initial SCr, diabetes, and chronic kidney disease) as covariates. The reduction of risk remained after adjusting for differences between groups (RR 0.61; 95% CI 0.39–0.93). Upon evaluation of a composite outcome of nephrotoxicity or dialysis, the outcome occurred in significantly fewer patients in the high-dose group, with 17.5% of patients in the low-dose group meeting this outcome, compared with 9.2% of patients in the high-dose group ($p < 0.01$; Figure 2).

Table 1. Baseline Characteristics

Demographics	≤ 20 mg/kg (n = 458)	>20 mg/kg (n = 469)	*p* Value
Male*	200 (43.7%)	159 (33.9%)	< 0.01
Age† (years)	77 (22)	80 (19)	0.04
Race*			0.80
Caucasian	341 (74.5%)	359 (76.6%)	
African American	104 (22.7%)	95 (20.3%)	
Asian	6 (1.3%)	8 (1.7%)	
Other	7 (1.5%)	7 (1.5%)	
Weight† (kg)	83.8 (35.5)	69 (24.7)	< 0.01
Height† (inches)	65 (6.1)	63.5 (5.9)	< 0.01
BMI† (kg/m^2)	29.9 (12.2)	26.1 (8.8)	< 0.01
Disease severity and comorbidities			
Initial SCr† (mg/dL)	2.5 (1.58)	2.07 (1.43)	< 0.01
Initial creatinine clearance† (mL/min)	20.3 (9.5)	21.0 (9.7)	0.22
Diabetes*	236 (51.5%)	156 (33.3%)	< 0.01
Chronic kidney disease*	256 (55.9%)	200 (42.6%)	< 0.01
Initial lactate† (mg/dL)	1.9 (2)	2.1 (2.2)	0.08
Acute kidney injury ICD-9 code present on admission*	364 (79.5%)	353 (75.3%)	0.13
Admitted to Intensive Care Unit*	190 (41.5%)	202 (43.1%)	0.63
Elixhauser Comorbidity Score†	17 (17)	17 (16)	0.73
Concomitant nephrotoxic medications			
Number that received a nephrotoxic medication*	357 (78.0%)	340 (72.5%)	0.06
Number of nephrotoxic medications†	1 (1)	1 (2)	0.02
Piperacillin-tazobactam*	159 (34.7%)	151 (32.2%)	0.42
Vancomycin dose characteristics			
Initial dose† (mg)	1250 (500)	1750 (500)	< 0.01
Initial weight-based dose† (mg/kg)	16.2 (3.3)	24.9 (4.9)	< 0.01
Continued on vancomycin therapy*	270 (59.0%)	261 (55.7%)	0.31
Number of vancomycin doses during hospital stay†	2 (2)	2 (2)	0.44
Received 5 or more doses of vancomycin*	72 (15.7%)	62 (13.2%)	0.28
Received 7 or more doses of vancomycin*	33 (7.2%)	31 (6.6%)	0.72
Order for pharmacist driven vancomycin dosing*	272 (59.4%)	249 (53.1%)	0.05
Trough goals for patients that received pharmacist driven vancomycin dosing (n = 521)			
Trough goal 10–15 μg/mL*	37 (13.6%)	13 (5.2%)	< 0.01
Trough goal 15–20 μg/mL*	235 (86.4%)	236 (94.8%)	< 0.01

BMI = body mass index; SCr = serum creatinine; ICD-9 = International Classification of Diseases, Ninth Revision.
* Number of patients (percentage total).
† Data are median values (interquartile range).

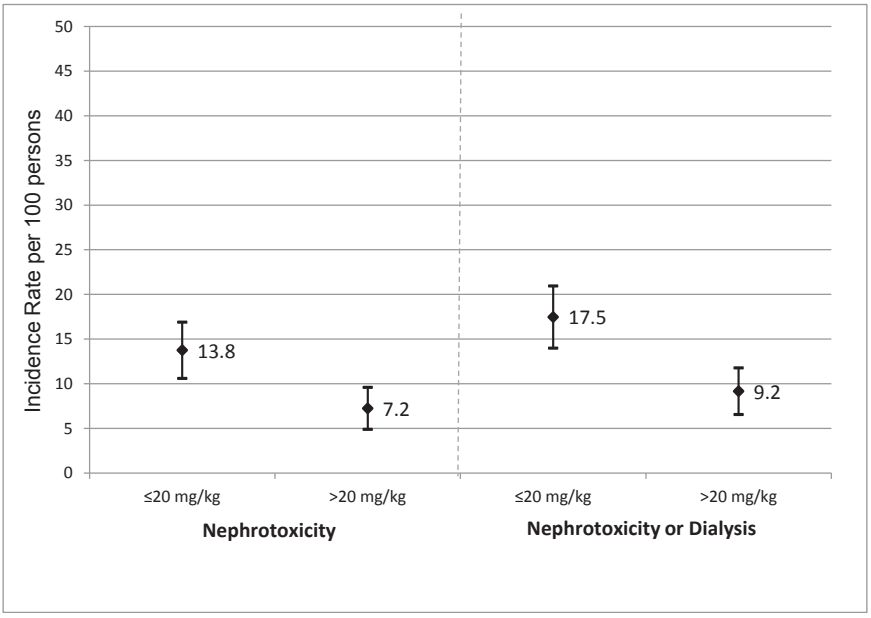

Figure 2. Incidence rates and 95% confidence intervals (CI). Rates of nephrotoxicity and rates of the composite outcome nephrotoxicity or dialysis with 95% confidence intervals.

Secondary Outcomes

In-hospital mortality and length of stay were not different between groups (Table 2). Vancomycin concentrations were evaluated and patients in the high-dose group had a lower occurrence of subtherapeutic vancomycin concentrations (<10 μg/mL) at any time during their hospital stay (14.3% vs. 31.7%, $p < 0.01$). The incidence of a supratherapeutic vancomycin concentration (>25 μg/mL at more than 20 h after the previous dose) was not different between the groups (2.1% high dose vs. 4.2% low dose).

Sensitivity analysis. To examine the sensitivity of our findings with the selection of a 20-mg/kg cut-off, a sensitivity analysis was conducted using a 25 mg/kg cut-off. These groups were less equally balanced, with 699 patients in the < 25-mg/kg group and 228 patients in the ≥ 25-mg/kg group. The median initial weight-adjusted dose was found to be 17.9 mg/kg (IQR 6.0) for the < 25-mg/kg group and 27.8 mg/kg (IQR 4.4) for the ≥ 25-mg/kg group ($p < 0.01$). A nonstatistically significant reduction was found when a dose cut-off of 25 mg/kg was utilized and the data were adjusted for group differences (RR 0.68, 95% CI 0.39–1.18).

Subgroup analysis. In a subgroup analysis, patients who received only one dose of vancomycin were examined separately from those who received two or more doses. There were 396 patients (396/927; 43%) who received only one dose. After adjustment for weight, age, sex, creatinine, diabetes, and chronic renal failure, the association between dosing group and nephrotoxicity was not statistically significant (RR 0.57; 95% CI 0.29–1.12). A similar nonstatistically significant reduction of risk was found when the subgroup with more than one dose of vancomycin was analyzed. For these 531 patients (531/927; 57%), after adjustment for weight, age, sex, creatinine, diabetes, and chronic renal failure, there was a 35% reduction in risk of nephrotoxicity (RR 0.65; 95% CI 0.38–1.14) with a loading dose, compared with no loading dose.

An additional analysis was completed to examine patients who received a longer duration of therapy after it was discovered that most patients were not continued on vancomycin. For patients who received five or more doses of vancomycin (134/927; 14%) after adjustment for weight, age, sex, creatinine, diabetes, and chronic renal failure, there was a 60% nonstatistically significant reduction in the risk of nephrotoxicity (RR 0.40; 95% CI 0.10–1.6) when patients received a loading dose, compared with no loading dose.

DISCUSSION

With an increasing emphasis on early and appropriate antibiotics, it is becoming essential to optimize dosing. This study provides evidence that a single high vancomycin loading dose does not increase the incidence in nephrotoxicity in those with impaired renal function. The notion of higher doses of vancomycin causing less nephrotoxicity seems counterintuitive, given studies that suggest large *daily* doses of vancomycin may be associated

Table 2. Secondary Outcomes

Secondary Outcomes	≤ 20 mg/kg (n = 458)	> 20 mg/kg (n = 469)	*p* Value
Hospital length of stay† (days)	6.7 (6.6)	6.5 (6.1)	0.30
Intensive care unit (ICU) admission*	190 (41.5%)	202 (43.1%)	0.63
ICU length of stay (hours) for those admitted to ICU only† (n = 392)	70 (89)	68.5 (89.8)	0.94
In-hospital mortality*	51 (11.1%)	61 (13.0%)	0.38
Dialysis order within 120 h of initial vancomycin dose*	28 (6.1%)	17 (3.6%)	0.08
Vancomycin concentrations			
Any concentration < 10 μg/mL*	145 (31.7%)	67 (14.3%)	< 0.01
>25 μg/mL at > 20 h from previous dose*	19 (4.2%)	10 (2.1%)	0.08
10–22 μg/mL between 22 and 26 h from previous dose*	111 (24.2%)	113 (24.1%)	0.96
15–22 μg/mL between 22 and 26 h from previous dose*	51 (11.1%)	59 (12.6%)	0.50

* Number of patients (percentage total).
† Data are median values (interquartile range).

with nephrotoxicity (9). Other studies, however, have not found increased rates of SCr elevation in patients receiving individual doses of vancomycin > 2000 mg (10). Increased vancomycin trough concentrations and duration of therapy beyond 14 days have previously been established as risk factors for nephrotoxicity (11,12). In the present study, when patients did not receive a high dose of vancomycin initially, they still developed nephrotoxicity, and at a higher rate compared with those who received high initial doses. Additionally, supratherapeutic levels did not differ between patients in the high- and low-dose groups. Based on our data, the theory that loading doses cause harm was not supported in this patient population. These findings may shift consideration toward maintenance dosing providing a greater impact in the development of nephrotoxicity.

Vancomycin is used empirically, and antimicrobial stewardship initiatives advocate for early discontinuation, often within 72 h in the absence of suspicion for a resistant organism (13,14). Although the short duration seen in this study may limit extrapolation to full treatment courses of vancomycin, these results may be more reflective of the first dose of vancomycin rather than toxicity that occurs with a prolonged course or improper maintenance dosing. Similar to the results found for the primary outcome, the subgroup analyses based on continuation of vancomycin therapy found a trend toward less nephrotoxicity in the high-dose group, suggesting that these results were not related to short courses of therapy. Although only a minority of patients received a full treatment course of vancomycin, this study's retrospective design illustrates the real-world use of the drug.

Nephrotoxicity rates in this study were higher than those generally reported with vancomycin monotherapy (5–7%), however, other studies have also reported higher rates of vancomycin-induced nephrotoxicity with general use (1,9,11,12). One could also argue that the population studied (CrCl < 30 mL/min) was at a higher risk of developing nephrotoxicity than the general population. In those with an initially high SCr, it is inherently difficult to define nephrotoxicity, as a 0.5-mg/dL rise in SCr may not be clinically significant compared with a percentage increase. Therefore, nephrotoxicity was chosen as the primary outcome, as opposed to acute kidney injury, which has a less robust definition of a 0.3-mg/dL rise (15). For the definition of nephrotoxicity chosen for this study, a time period of 120 h was selected to capture as many cases of nephrotoxicity caused by a loading dose as possible, while attempting to minimize confounders that may arise throughout hospitalization, given that three SCr values were required to assess the primary outcome.

Similar results of decreased nephrotoxicity with higher doses have been reported in sepsis patients who received vancomycin in the ED (7). Patients who received > 20 mg/kg of vancomycin had an incidence of nephrotoxicity of 5.8%, compared with 11.1% in those who received a lower dose of ≤ 20 mg/kg ($p < 0.001$). The authors suggested that progression of sepsis should be considered with under-dosing of antibiotic therapy. The results of this prior study, compared with the current study, showed slightly higher incidences of nephrotoxicity throughout the population with reduced renal function, but still less nephrotoxicity in those that received an initial dose of vancomycin > 20 mg/kg.

As further data emerge surrounding the utility and safety of vancomycin loading doses, this study can serve as evidence that patients with renal dysfunction can safely receive loading doses of vancomycin. Inclusion of patients with renal dysfunction into prospective trials that provide vancomycin loading doses is likely safe and would allow further evidence into optimal dosing strategies. Ideally, the most compelling evidence to provide a loading dose of vancomycin will come from investigation into the differences in clinical course and mortality outcomes.

Limitations

The retrospective nature of this study carries the potential for confounding and selection bias. Although the intervention and comparator groups were similar in size, there were differences in characteristics between the groups that were addressed via model adjustment. Consensus guidelines have proposed a definition for vancomycin-induced nephrotoxicity; however, this definition was not able to be implemented in its entirety (1). Any two SCr levels that met the threshold were used in the nephrotoxicity definition instead of two serial SCr values. This was less restrictive and captured as many potential instances of nephrotoxicity as possible. Although a large sample size was achieved by this study, it was conducted at a single health system and may not be generalizable. Additionally, the subsequent vancomycin dosing regimen was not evaluated and may have confounded the association in the primary outcome.

CONCLUSION

ED patients with CrCl < 30 mL/min that received a loading dose of vancomycin did not have a higher incidence of nephrotoxicity compared with those receiving a lower initial dose. The decreased rate of nephrotoxicity in those who received a vancomycin dose > 20 mg/kg suggests that providing loading doses in patients with severe renal dysfunction is likely safe. In patients with severe infection and CrCl < 30 mL/min, it is reasonable to consider loading doses of vancomycin that are consistent with guidelines.

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REFERENCES

1. 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 American, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66:82–98.
2. Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. Crit Care Clin 2011; 27:19–34.
3. Davis SL, Scheetz MH, Bosso JA, Goff DA, Rybak MJ. Adherence to the 2009 consensus guidelines for vancomycin dosing and monitoring practices: a cross-sectional survey of U.S. hospitals. Pharmacotherapy 2013;33:1256–63.
4. Hall AB, Montero J, Cobian J, Regan T. The effects of an electronic order set on vancomycin dosing in the ED. Am J Emerg Med 2015; 33:92–4.
5. Rosini JM, Laughner J, Levine BJ, Papas MA, Reinhardt JF, Jasani NB. A randomized trial of loading vancomycin in the emergency department. Ann Pharmacother 2015;49:6–13.
6. Reardon J, Lau TTY, Ensom MHH. Vancomycin loading doses: a systematic review. Ann Pharmacother 2015;49:557–65.
7. Rosini JM, Davis JJ, Muenzer J, et al. High single-dose vancomycin loading is not associated with increased nephrotoxicity in emergency department sepsis patients. Acad Emerg Med 2016; 23:744–6.
8. StataCorp. Stata Statistical Software: Release 12.1. College Station, TX: Statacorp LP; 2017.
9. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. Antimicrobial Agents Chemother 2008;52:1330–6.
10. Mansour H, Bush JA, Brito M, et al. The effect of vancomycin doses greater than 2 grams on serum creatinine and vancomycin trough levels. Int J Pharm Pharm Sci 2014;6:621–5.
11. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant *Staphylococcus aureus* pneumonia. Clin Ther 2007; 29:1107–15.
12. Hall RG, 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;14:12.
13. Barlam TF, Cosgrove SE, Abbo LM, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis 2016;62:e51–77.
14. Connor DM, Binkley S, Fishman NO, Gasink LB, Linkin D, Lautenbach E. Impact of automatic orders to discontinue vancomycin therapy on vancomycin use in an antimicrobial stewardship program. Infect Control Hosp Epidemiol 2007;28: 1408–10.
15. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1–138.

ARTICLE SUMMARY

1. Why is this topic important?

Consensus guidelines recommend loading doses of vancomycin to quickly attain target trough concentrations of 15–20 μg/mL in critically ill patients. Although loading doses are recommended to optimize efficacy, nephrotoxicity is often questioned. The literature is limited regarding the safety of loading doses in patients with underlying renal dysfunction.

2. What does this study attempt to show?

This study suggests that vancomycin loading doses do not increase nephrotoxicity compared with lower doses in patients with severe renal dysfunction and should be considered in these patients.

3. What are the key findings?

Patients in the loading dose group had a reduced risk of nephrotoxicity (relative risk 0.53; 95% confidence interval 0.35–0.78). The reduction in risk remained after fitting a generalized linear model adjusting for weight, age, sex, initial serum creatinine, diabetes, and chronic kidney disease (relative risk 0.61; 95% confidence interval 0.39–0.93).

4. How is patient care impacted?

Achieving vancomycin target serum concentrations faster in patients with severe renal dysfunction may improve outcomes.