Vancomycin-Associated Nephrotoxicity: The Obesity Factor

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Abstract

Background: Current recommendations suggest that vancomycin dosing utilize actual rather than ideal body weight in obese patients. Thus, obese patients may be at greater risk for nephrotoxicity. The purpose of this study was to compare the incidence of nephrotoxicity in vancomycin-treated obese and lean patients at our institution, where unadjusted, actual body weight-based dosing (capped at 2 g per dose twice daily) is used. We expected obese patients to experience a greater incidence of nephrotoxicity than lean patients.

Methods: This study examined a retrospective cohort of patients treated with vancomycin for gram-positive or mixed infections in our facility from 2005–2009 who were not receiving hemodialysis at the time of admission. Patients were stratified by body mass index (BMI; obese ≥ 30 kg/m² vs. lean < 30 kg/m²). Relative risk (RR), 95% confidence intervals (CIs), and p values were computed using a generalized estimating equation to accommodate a correlated data structure corresponding to multiple episodes of infection per individual. Multivariable analysis was performed.

Results: A total of 530 patients (207 obese; 323 lean) with 1,007 episodes of infection were treated with vancomycin. Patient demographics, co-morbidities, sites of infection, and infecting organisms were similar in the two groups. Female gender ($p=0.042$), diabetes mellitus (DM) ($p=0.018$), and hypertension (HTN) ($p=0.0009$) were more often associated with obesity, whereas allografts ($p=0.022$) and peripheral vascular disease ($p=0.036$) were more often present in lean patients. The Acute Physiology and Chronic Health Evaluation II score > 21 was the only variable associated with nephrotoxicity ($p=0.039$). After adjusting for statistically significant variables, obesity was found not to be associated with a greater risk of nephrotoxicity (RR = 0.98; 95% CI = 0.93–1.04; $p=0.59$).

Conclusion: No difference in nephrotoxicity was observed between lean and obese patients treated with vancomycin at our institution.

VANCOMYCIN WAS ORIGINALLY INTRODUCED in the MID-1950s as a combatant to penicillin-resistant staphylococcal infections [1]. Because of early manufacturing impurities believed to contribute to a multitude of adverse effects, including nephrotoxicity, the drug was quickly dubbed “Mississippi mud” [2,3]. These impurities have since been eliminated, and current nephrotoxic associations may be attributable to misuse of the drug outside of recommended guidelines [4,5].

More than one-third of American adults are obese (i.e., have a body mass index [BMI] > 30 kg/m²) [6,7]. Obesity has been linked to diabetes mellitus (DM), hypertension (HTN), and dyslipidemia (i.e., metabolic syndrome) [8–10]. Diabetes

mellitus and HTN are associated with nephrotoxicity; however, obesity also may play a unique role through lipid-induced nephropathy [11,12].

Current recommendations suggest vancomycin dosing utilize actual rather than ideal body weight in obese patients because of the accelerated renal clearance in this population [13–20]. Additionally, an increase in multi-drug-resistant bacteria and poor penetrance into certain tissues (e.g., lung) has resulted in greater vancomycin therapeutic ranges [21]. Thus, obese patients may be at greater risk for nephrotoxicity. The purpose of this study was to compare the incidence of nephrotoxicity in vancomycin-treated obese and lean patients at our institution, where unadjusted, actual body weight-

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based dosing is used. We hypothesized that obese patients would experience a greater incidence of nephrotoxicity than lean patients.

Patients and Methods

Study design

Institutional Review Board approval was obtained prior to data analysis. Details of the database and methodology have been described and are summarized below [5].

This was a retrospective analysis of a prospectively maintained database of all surgical patients (e.g., general, abdominal organ transplant, and trauma) admitted to a level I trauma and tertiary-care center from 1996 to 2012 and treated for sepsis. For the purposes of this study, we queried the database for all patients treated with vancomycin from December 6, 2005–December 4, 2009; body mass index (BMI) data were unobtainable for dates prior to this. Patients receiving hemodialysis prior to vancomycin initiation were excluded. Included patients were then stratified by BMI (i.e., BMI ≥ 30 kg/m² vs. <30 kg/m²). Demographics and co-morbidities, sites of infection, causative organisms, and outcomes were compared for the two groups.

Database

Patient data were collected prospectively every other day by medical chart and laboratory review and patient interview and examination. Unique episodes of infection were identified for each patient and classified as separate if positive cultures were present more than 72 h apart. Sites of infection, antibiotic therapy and duration, and organisms determined by culture were recorded for each episode of infection.

Patients

Gender, age, race (patient-defined), solid organ transplant, trauma, DM, HTN, hyperlipidemia (HLD), cardiovascular disease, peripheral vascular disease (PVD), pulmonary disease, ventilator dependence, renal insufficiency (RI), initial creatinine concentration, initial estimated glomerular filtration rate (eGFR), hepatic insufficiency, malignant disease, chronic steroid use, prior transfusion during the same hospitalization, nosocomial infection, patient location at the time of infection, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and concomitant treatment with purported nephrotoxic antibiotics (i.e., aminoglycosides, amphotericin B, and piperacillin-tazobactam) were evaluated at the time of the initial infectious episode. New-onset or change in ventilator dependence, RI, HD, transfusion, patient location, APACHE II score, and concomitant treatment with purported nephrotoxic antibiotics were measured at the time of each subsequent infectious episode. Similarly, sites of infection and the organisms cultured were recorded at the time of each infectious episode. Outcomes included the total number of infectious episodes treated with vancomycin, the total number of antibiotics used per infectious episode, the duration of vancomycin treatment per episode, the maximum vancomycin trough concentration per episode, maximum creatinine concentration during vancomycin treatment per episode, final creatinine concentration after vancomycin treatment per episode, change in creatinine concentration during vancomycin treatment (i.e., maximum creatinine –

initial creatinine) and after vancomycin treatment (i.e., final creatinine – initial creatinine), lowest eGFR during vancomycin treatment per episode, final eGFR after vancomycin treatment per episode, nephrotoxicity per episode, new-onset hemodialysis during vancomycin treatment, hospital length of stay (HLOS), and death. Patients were followed until death or hospital discharge.

Setting

As previously mentioned, the University of Virginia Health System is a level I trauma and tertiary-care center. In general, our pharmacy department doses vancomycin on the basis of total body weight (15 mg/kg every 12 h for patients with normal renal function) and estimated renal function. However, the total initial empiric dose is capped at around 1,750–2,000 mg/dose. A trough is measured prior to the fourth dose, and the regimen is adjusted to achieve a trough concentration of 10–20 mcg/mL (10–15 mcg/mL for less severe infections and 15–20 mcg/mL for methicillin-resistant *Staphylococcus aureus* [MRSA], osteomyelitis, endocarditis, meningitis, sepsis, and other severe infections).

Definitions

The infection criteria were those of the U.S. Centers for Disease Control and Prevention [22]. Solid organ transplant was defined as kidney, liver, pancreas, heart, lung, kidney/pancreas, liver/pancreas, or small bowel transplantation. Pulmonary disease was defined as active treatment for lung disease being given prior to hospital admission. Renal insufficiency was defined as a serum creatinine concentration ≥ 2.0 mg/dL at time of an infectious episode. Patient location at time of an infectious episode was defined as home, hospital ward, intensive care unit (ICU), or other. Initial creatinine concentration and eGFR were recorded immediately prior to vancomycin initiation per infectious episode. Other co-morbidities were defined by chart documentation, medication history, or patient examination. Vancomycin trough concentrations were defined as the greatest trough concentration documented in the patient's chart during the treatment period. Nephrotoxicity was defined as a 0.5 mg/dL increase in the serum creatinine concentration, a 50% increase in baseline serum creatinine concentration, or a 50% decrease in the baseline creatinine clearance [23–26]. Endpoints of vancomycin therapy included culture-proved resistance or insensitivity, adequate treatment duration as defined by unit guidelines and specific to the site of infection (i.e., lung [8–14 d], abdomen [5–7 d], vascular catheter [5 d], urine [5–7 d], skin and skin structure (until resolution of surrounding cellulitis), and blood stream [10–14 d]), or death. Uncomplicated blood stream infections involving *S. aureus* and a treatable focus were treated for 14 d following culture-proved clearance. Complicated blood stream infections involving *S. aureus* (e.g., infected endovascular grafts, endocardial vegetation) were treated for 4–6 wks after culture-proved clearance. Death was defined as that from any cause after infection diagnosis while the patient was hospitalized.

Statistical analysis

Demographics and co-morbidities, infection sites, infection organisms, and outcomes were compared in the obese and lean groups. Relative risk (RR), 95% confidence intervals

(CI), and *p* values were computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber White “sandwich variance” estimates) to accommodate a correlated data structure corresponding to multiple episodes of infection per individual [27,28]. Variables deemed statistically significant ($p < 0.05$) for either obesity or nephrotoxicity, among the demographics and co-morbidities, infection sites, and infection-related organisms, were included in the multivariable log-binomial regression model. A subset analysis evaluating nephrotoxic risk assigned to vancomycin trough concentration and stratified by obesity also was performed. Analysis was performed using SAS Version 9.3[®] (SAS Institute, Cary, NC) programming software. Statistical significance was defined as a *p* value of < 0.05 .

Results

A total of 530 patients with 1,007 episodes of infection were treated with vancomycin from December 6, 2005–December 4, 2009. Of these, 207 patients with 389 episodes of infection were obese. On average, each obese patient experienced 1.8 ± 1.3 episodes of infection that were treated with vancomycin, whereas each lean patient experienced 1.8 ± 1.1 episodes of infection treated with vancomycin ($p = 0.62$). Additionally, each obese patient was treated on average with 3.5 ± 1.4 antibiotics (including vancomycin) per infectious episode, whereas each lean patient was treated with 3.6 ± 1.4 antibiotics (including vancomycin) per infectious episode ($p = 0.71$).

Demographics and co-morbidities stratified by obesity and each variable's association with obesity and nephrotoxicity are listed in Table 1. Female gender, DM, and HTN were more often associated with obesity, whereas transplant and PVD were more often associated with lean patients. The APACHE II score (> 21) was the only variable associated with nephrotoxicity. Of note, concomitant treatment with other purportedly nephrotoxic antibiotics (i.e., aminoglycosides, amphotericin B, and piperacillin-tazobactam) was not associated with nephrotoxicity.

Sites of infection stratified by obesity and each variable's association with obesity and nephrotoxicity are listed in Table 2. Sites of infection were not observed to be associated with obesity. Additionally, sites of infection were not associated with nephrotoxicity.

Culture-proved organisms stratified by patient obesity and each variable's association with obesity and nephrotoxicity are listed in Table 3. Organisms causing infection were not associated with obesity. However, *Pseudomonas aeruginosa* and vancomycin-resistant enterococcus (VRE) were protective against nephrotoxicity. Additionally, *Escherichia coli*-related infections trended toward a protective association, whereas *Clostridium difficile*-related infections trended toward a greater nephrotoxic association.

Patient outcomes stratified by obesity are listed in Table 4. Patients were treated with vancomycin for similar durations (obese 8.4 ± 7.6 days vs. lean 9.1 ± 9.6 days; $p = 0.94$) and were hospitalized for a similar period of time (obese 24 ± 25 days vs. lean 24 ± 32 days; $p = 0.64$) in the two groups. No difference between groups was observed regarding vancomycin trough concentrations ($p = 0.80$), change in serum creatinine concentration (maximum – initial; $p = 0.59$; final – initial; $p = 0.37$), nephrotoxicity ($p = 0.92$), new-onset hemodialysis ($p = 0.45$), or death ($p = 0.77$) during vancomycin

treatment. Furthermore, a subset analysis evaluating nephrotoxic risk and vancomycin trough concentration revealed that only supratherapeutic troughs (> 20 mcg/mL) approached a significant association with nephrotoxicity ($p = 0.054$). After adjusting for statistically significant variables in Tables 1–3 (i.e., gender, transplant, DM, HTN, PVD, APACHE II score, *Pseudomonas aeruginosa*, and VRE), obesity was not associated with a greater risk for nephrotoxicity than was lean status (RR = 0.93; 95% CI = 0.93–1.04; $p = 0.59$) (conclusion not shown in the tables).

Discussion

We present one of the largest cohorts published to date evaluating vancomycin, obesity, and nephrotoxicity [13–19,29–31]. Our study observed a 21% incidence of nephrotoxicity (obese = 18% vs. lean = 23%) among infectious episodes treated with vancomycin and a 12% incidence of new-onset hemodialysis (obese = 10% vs. lean = 14%). However, the mean creatinine and eGFR values measured at the completion of antibiotic therapy indicated that the nephrotoxicity had resolved for the most part. These results fall within previously reported nephrotoxicity ranges of 2.9%–43% among similar populations [15,25,29,32–36].

Vancomycin's nephrotoxicity is theorized to be secondary to oxidative stress and free-radical generation in the proximal renal tubule, resulting in cellular necrosis [23,25]. The degree of the effect may be enhanced by prolonged therapy (i.e., 7–14 d) or concomitant nephrotoxic risk factors (i.e., critical illness or the administration of radiopaque contrast agents or other nephrotoxic antibiotics) [23,25,36]. Although the difference was not statistically significant, lean patients experienced longer vancomycin treatment durations, had greater APACHE II scores, and were more often hospitalized in the ICU or recipients of blood transfusions than were obese patients. However, ICU location and prior blood transfusion were not associated with nephrotoxicity on univariable analysis. Additionally, concomitant treatment with other purported nephrotoxic antibiotics (i.e., aminoglycosides, amphotericin B, and piperacillin-tazobactam) was not associated with nephrotoxicity on univariable analysis. Furthermore, after adjusting for APACHE II scores, no difference was apparent in the nephrotoxicity incidence in the two groups. Our results are supported by previous studies that failed to find an association between co-morbidity, concomitant treatment with purported nephrotoxic agents, and vancomycin-induced nephrotoxicity [23,37].

Infection location has been associated with vancomycin-induced nephrotoxicity. For example, pulmonary penetrance may be poor when treating infections of the lung owing to the need for passive transport across two membrane barriers and lymphatic clearance [21,38,39]. This would necessitate higher doses of the drug to reach adequate target concentrations, potentially resulting in a greater incidence of nephrotoxicity. Although the difference was not statistically significant, lean patients in our study had a greater prevalence of lung infections. However, infections of the lung were not associated with nephrotoxicity on univariable analysis. Additional types of infection requiring greater vancomycin trough concentrations and associated with a greater risk of nephrotoxicity are meningitis, endocarditis, and osteomyelitis [23].

Pseudomonas, VRE, and *E. coli*-related infections were protective against nephrotoxicity on univariable analysis.

TABLE 1. DEMOGRAPHICS AND CO-MORBIDITIES^c STRATIFIED BY OBESITY AND UNADJUSTED LOG-BINOMIAL REGRESSION ANALYSIS OF OBESITY AND NEPHROTOXICITY

<i>Demographics/ Co-Morbidities</i>	<i>Lean n (%)</i>	<i>Obese n (%)</i>	<i>RR (95% CI); P^{a,b} (Obesity)</i>	<i>RR (95% CI); P^{a,c} (Nephrotoxicity)</i>
No. of patients	323 (61)	207 (39)	—	—
No. of infectious episodes	618 (61)	389 (39)	—	—
Gender ^d				
Male	415 (67)	214 (55)	1.0 ref	1.0 ref
Female	203 (33)	175 (45)	1.1 (1.002–1.1); 0.042	0.98 (0.93–1.03); 0.36
Age (years)				
Mean ± SD	56 ± 17	54 ± 14	0.071	
Median (IQR)	55 (23)	55 (21)		
Q1 (≤45)	84 (26)	57 (28)	1.0 ref	1.0 ref
Q2 (46–55)	75 (23)	60 (29)	1.1 (0.95 –1.3); 0.17	1.03 (0.95–1.1); 0.52
Q3 (56–67)	73 (23)	56 (27)	1.1 (0.95 –1.2); 0.32	1.04 (0.96–1.1); 0.34
Q4 (>67)	89 (28)	34 (16)	0.96 (0.85 –1.1); 0.46	1.01 (0.93–1.1); 0.83
Race				
White	538 (87)	332 (85)	1.0 ref	1.0 ref
Black	67 (11)	54 (14)	1.04 (0.98 –1.1); 0.22	0.95 (0.85–1.1); 0.36
Other	5 (1)	1 (0)	0.98 (0.89 –1.1); 0.66	1.2 (0.92–1.6); 0.18
Hispanic	8 (1)	2 (1)	0.96 (0.86 –1.1); 0.55	1.1 (0.91–1.4); 0.27
Transplant ^{d,e}				
No	472 (76)	346 (89)	1.0 ref	1.0 ref
Yes	146 (24)	43 (11)	0.94 (0.89 –0.99); 0.022	1.1 (0.98–1.1); 0.13
Trauma				
No	488 (85)	304 (87)	1.0 ref	1.0 ref
Yes	83 (15)	47 (13)	0.99 (0.93 –1.05); 0.67	0.94 (0.85–1.03); 0.20
Diabetes mellitus ^d				
No	501 (81)	274 (70)	1.0 ref	1.0 ref
Yes	117 (19)	115 (30)	1.1 (1.02 –1.3); 0.018	1.04 (0.93–1.2); 0.49
Hypertension ^d				
No	430 (70)	189 (49)	1.0 ref	1.0 ref
Yes	188 (30)	200 (51)	1.1 (1.02 –1.1); 0.0009	1.1 (0.99–1.1); 0.13
Hyperlipidemia				
No	538 (87)	325 (84)	1.0 ref	1.0 ref
Yes	80 (13)	64 (16)	1.2 (0.99 –1.4); 0.075	1.03 (0.94–1.1); 0.55
Cardiovascular disease				
No	464 (75)	289 (74)	1.0 ref	1.0 ref
Yes	154 (25)	100 (26)	1.1 (0.95 –1.2); 0.22	1.001 (0.94–1.1); 0.98
Peripheral vascular disease ^d				
No	584 (95)	377 (97)	1.0 ref	1.0 ref
Yes	34 (6)	12 (3)	0.63 (0.41 –0.97); 0.036	1.1 (0.91–1.2); 0.51
Pulmonary disease				
No	542 (88)	318 (82)	1.0 ref	1.0 ref
Yes	76 (12)	71 (18)	0.96 (0.84 –1.1); 0.62	0.98 (0.90–1.1); 0.72
Ventilator dependence				
No	470 (76)	292 (75)	1.0 ref	1.0 ref
Yes	148 (24)	97 (25)	1.001 (0.99 –1.01); 0.85	0.95 (0.86–1.05); 0.32
Renal insufficiency				
No	576 (93)	362 (93)	1.0 ref	1.0 ref
Yes	42 (7)	27 (7)	0.94 (0.82 –1.1); 0.33	0.96 (0.82–1.1); 0.61
Initial creatinine concentration (mg/dL)				
Mean ± SD	1.3 ± 0.93	1.3 ± 1.0	0.57	
Median (IQR)	1.0 (0.70)	1.0 (0.70)		
≤1.0	333 (54)	213 (55)	1.0 ref	1.0 ref
1.1–1.5	137 (22)	87 (22)	1.01 (0.95 –1.1); 0.76	0.99 (0.89–1.1); 0.78
1.6–2.0	61 (10)	39 (10)	1.01 (0.96 –1.05); 0.80	0.998 (0.94–1.2); 0.98
>2.0	87 (14)	50 (13)	0.99 (0.94 –1.04); 0.63	1.020 (0.89–1.2); 0.79

(continued)

TABLE 1. (CONTINUED)

<i>Demographics/ Co-Morbidities</i>	<i>Lean n (%)</i>	<i>Obese n (%)</i>	<i>RR (95% CI); P^{a,b} (Obesity)</i>	<i>RR (95% CI); P^{a,c} (Nephrotoxicity)</i>
Initial eGFR (mL/min/1.73 m ²)				
> 60	388 (63)	236 (61)	1.0 ref	1.0 ref
31–60	145 (23)	104 (27)	1.01 (0.96–1.1); 0.64	0.97 (0.88 –1.1); 0.61
15–30	73 (12)	28 (7)	0.99 (0.95–1.03); 0.53	1.1 (0.94 –1.2); 0.30
(<15)	12 (2)	21 (5)	1.02 (0.96–1.1); 0.57	0.93 (0.72 –1.2); 0.59
Hepatic insufficiency				
No	576 (93)	376 (97)	1.0 ref	1.0 ref
Yes	42 (7)	13 (3)	1.1 (0.93–1.2); 0.39	1.1 (0.88 –1.3); 0.44
Malignant disease				
No	554 (90)	329 (85)	1.0 ref	1.0 ref
Yes	64 (10)	60 (15)	1.01 (0.98–1.04); 0.62	0.93 (0.80 –1.1); 0.37
Chronic steroid use				
No	447 (72)	334 (86)	1.0 ref	1.0 ref
Yes	171 (28)	55 (14)	0.94 (0.83–1.1); 0.31	1.1 (0.99 –1.2); 0.092
Prior transfusion				
No	372 (60)	245 (63)	1.0 ref	1.0 ref
Yes	246 (40)	144 (37)	0.99 (0.94–1.04); 0.60	0.99 (0.94 –1.1); 0.84
Nosocomial infection				
No	177 (29)	133 (34)	1.0 ref	1.0 ref
Yes	441 (71)	256 (66)	0.98 (0.93–1.03); 0.41	1.01 (0.92 –1.1); 0.91
Patient location				
Home	177 (29)	131 (34)	1.0 ref	1.0 ref
Hospital ward	172 (28)	104 (27)	1.004 (0.97–1.04); 0.81	1.003 (0.90 –1.1); 0.96
ICU	219 (35)	132 (34)	0.99 (0.97–1.02); 0.64	0.999 (0.91 –1.1); 0.99
Other	50 (8)	22 (6)	1.002 (0.88–1.1); 0.97	1.04 (0.92 –1.2); 0.54
APACHE II score ^d				
Mean ± SD	17 ± 7.5	17 ± 8.2	0.77	
Median (IQR)	16 (10)	16 (10)		
Q1 (≤11)	172 (28)	110 (28)	1.0 ref	1.0 ref
Q2 (12–16)	140 (23)	88 (23)	0.99 (0.93–1.1); 0.82	0.96 (0.85 –1.1); 0.50
Q3 (17–21)	153 (25)	96 (25)	1.02 (0.95–1.1); 0.65	0.96 (0.86 –1.1); 0.50
Q4 (>21)	153 (25)	95 (24)	1.01 (0.95–1.1); 0.84	1.1 (1.006–1.2); 0.039
Concomitant nephrotoxic abx ^f				
No	248 (40)	156 (40)	1.0 ref	1.0 ref
Yes	370 (60)	233 (60)	0.99 (0.98–1.01); 0.46	1.01 (0.94 –1.09); 0.75

^aTo accommodate the correlated data structure corresponding to multiple episodes of infection per individual, the analysis of obesity^b and nephrotoxicity^c among episodes of infection was computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber-White “sandwich variance” estimates).

^dVariables included in the multivariable analysis.

^eTransplants (analyzed by patient) included 24 kidney, 58 liver, two pancreas, nine kidney/pancreas, two liver/kidney, and one small bowel.

^fConcomitant nephrotoxic antibiotics included aminoglycosides, amphotericin B, and piperacillin-tazobactam.

abx = antibiotics. APACHE = Acute Physiology and Chronic Health Evaluation; CI = confidence interval; eGFR = estimated glomerular filtration rate; ICU = intensive care unit; IQR = interquartile range; Q = quartile; RR = relative risk; SD = standard deviation.

Once sensitivity testing was completed, de-escalation of antimicrobial therapy would occur, thus minimizing any unnecessary potentially nephrotoxic exposure. Conversely, if microorganisms were determined to be susceptible to potentially nephrotoxic agents, a longer duration of treatment may be required, thereby increasing the risk of nephrotoxicity.

Current guidelines recommend treatment with vancomycin using doses of 15–20 mg/kg based on actual body weight, given every 8–12 h, in patients with normal renal function, thus maximizing the frequency of trough concentrations between 10 mg/L and 20 mg/L [4]. This range reduces the incidence of both nephrotoxicity and drug resistance [4]. Although the difference was not statistically significant, lean

patients in our study showed slightly greater vancomycin trough concentrations than obese patients. However, both groups had trough concentrations within the recommended range. Additionally, using a cycling antibiotic protocol, our group previously compared 298 vancomycin-treated patients (571 infectious episodes) with 247 linezolid-treated patients (475 infectious episodes) [5], observing a similar nephrotoxic profile in the two groups when patients were treated to within the 10–20 mg/L trough range, even among critically ill patients with complex infections.

Lipid-induced nephrotoxicity was first described in the late 1970s and early 1980s [12,40]. Kuo et al. evaluated cephazolidine-induced nephrotoxicity in male Fischer 344 rats and

TABLE 2. SITES OF INFECTION (VARIABLES/INFECTIOUS EPISODE) STRATIFIED BY OBESITY AND UNADJUSTED LOG-BINOMIAL REGRESSION ANALYSIS OF OBESITY AND NEPHROTOXICITY

<i>Sites</i>	<i>Lean n (%)</i>	<i>Obese n (%)</i>	<i>RR (95% CI); P^{a,b} (Obesity)</i>	<i>RR (95% CI); P^{a,c} (Nephrotoxicity)</i>
Number of patients	323 (61)	207 (39)	—	—
Number of infectious episodes	618 (61)	389 (39)	—	—
Central nervous system				
No	617 (100)	389 (100)	—	—
Yes	1 (0)	0		
Peritoneum				
No	476 (77)	293 (75)	1.0 Referent	1.0 Referent
Yes	142 (23)	96 (25)	0.999 (0.98 –1.01); 0.87	0.996 (0.95 –1.04); 0.87
Upper GI				
No	615 (100)	388 (100)	1.0 Referent	1.0 Referent
Yes	3 (0)	1 (0)	1.0002 (0.99 –1.01); 0.97	0.93 (0.77 –1.1); 0.42
Colon				
No	584 (95)	374 (96)	1.0 Referent	1.0 Referent
Yes	34 (6)	15 (4)	0.995 (0.99 –1.002); 0.16	1.1 (0.998–1.2); 0.058
Lung				
No	472 (76)	311 (80)	1.0 Referent	1.0 Referent
Yes	146 (24)	78 (20)	1.01 (0.99 –1.03); 0.21	0.997 (0.96 –1.04); 0.89
Pleura				
No	611 (99)	387 (99)	1.0 Referent	1.0 Referent
Yes	7 (1)	2 (1)	1.0001 (0.99 –1.01); 0.98	0.90 (0.73 –1.1); 0.30
Skin/soft tissue				
No	582 (94)	354 (91)	1.0 Referent	1.0 Referent
Yes	36 (6)	35 (9)	1.01 (0.996–1.02); 0.21	0.96 (0.89 –1.03); 0.25
Incision				
No	558 (90)	339 (87)	1.0 Referent	1.0 Referent
Yes	60 (10)	50 (13)	0.99 (0.97 –1.01); 0.44	0.9997 (0.95 –1.1); 0.99
Line				
No	598 (97)	377 (97)	1.0 Referent	1.0 Referent
Yes	20 (3)	12 (3)	1.01 (0.99 –1.03); 0.32	1.03 (0.95 –1.1); 0.47
Blood				
No	519 (84)	331 (85)	1.0 Referent	1.0 Referent
Yes	99 (16)	58 (15)	1.002 (0.99 –1.01); 0.67	0.98 (0.94 –1.009); 0.16
Urine				
No	550 (89)	350 (90)	1.0 Referent	1.0 Referent
Yes	68 (11)	39 (10)	0.99 (0.97 –1.01); 0.16	1.02 (0.99 –1.1); 0.23

^aTo accommodate a correlated data structure corresponding to multiple episodes of infection per individual, the analysis of obesity^b and nephrotoxicity^c among episodes of infection was computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber-White “sandwich variance” estimates).

CI=confidence interval; GI=gastrointestinal; RR=relative risk.

female New Zealand White rabbits [40]. They observed an increase in lipid peroxidation specifically in renal cortical cells. Additionally, by removing selenium or vitamin E, known antioxidants, from the diet, lipid peroxidation was increased, along with nephrotoxicity. Although the pathophysiological link between dyslipidemia and nephrotoxicity remains poorly defined, recent studies continue to lend support to this theory [11,41–45]. The results suggest that glomerulosclerosis and tubulointerstitial lesions, together with accelerated atherosclerosis attributable to dyslipidemia, may be the contributory factor to the progression of renal insufficiency [11,42,44,45]. Additionally, adipose tissue is a source of inflammatory cytokines (e.g., tumor necrosis factor- α , interleukin-6, leptin, and C-reactive protein), which may potentiate oxidative stress at the renal tubular level [11,43–45]. Notably, DM, HTN, and dyslipidemia were more prevalent among obese patients in our

study group; however, these variables were not associated with nephrotoxicity on univariable analysis.

Pharmacokinetic dosing is based on drug absorption, distribution, metabolism, and excretion [16]. Depending on the lipophilicity of the drug, obese patients would be expected to have a larger volume of distribution. Although vancomycin is considered to be hydrophilic, approximately 30% of adipose tissue is water [18]. Thus, an increase in adipose tissue, combined with an increase in protein mass, could bind vancomycin, thereby reducing the unbound, active drug concentration in the circulation. Additionally, obese patients experience a renal clearance increase secondary to higher cardiac output, blood flow, and blood volume. As previously mentioned, current recommendations suggest that vancomycin dosing utilize total body weight (TBW) [13–20]. In contrast, Reynolds et al. retrospectively compared an original

TABLE 3. ORGANISMS STRATIFIED BY OBESITY AND UNADJUSTED LOG-BINOMIAL REGRESSION ANALYSIS OF OBESITY AND NEPHROTOXICITY

Organism	Lean n (%)	Obese n (%)	RR (95% CI); P ^{a,b} (Obesity)	RR (95% CI); P ^{a,b,c} (Nephrotoxicity)
Number of patients	323 (61)	207 (39)	—	—
Number of infectious episodes	618 (61)	389 (39)	—	—
Fungal	88 (14)	62 (16)	1.001 (0.98 –1.02); 0.93	0.98 (0.92 –1.05); 0.56
<i>Candida albicans</i>	39 (6)	22 (6)	0.996 (0.99 –1.003); 0.24	0.94 (0.86 –1.03); 0.19
<i>Candida glabrata</i>	35 (6)	17 (4)	1.02 (0.98 –1.1); 0.41	1.04 (0.95 –1.1); 0.42
Gram-negative bacteria	212 (34)	151 (39)	0.998 (0.98 –1.01); 0.82	0.99 (0.94 –1.05); 0.81
<i>Escherichia coli</i>	53 (9)	45 (12)	1.004 (0.998–1.01); 0.21	0.94 (0.88 –1.01); 0.076
<i>Klebsiella pneumonia</i>	42 (7)	24 (6)	1.01 (0.98 –1.04); 0.49	1.01 (0.90 –1.1); 0.92
<i>Serratia</i> spp.	6 (1)	9 (2)	1.01 (0.99 –1.03); 0.20	1.02 (0.72 –1.4); 0.92
<i>Pseudomonas aeruginosa</i> ^d	29 (5)	26 (7)	0.99 (0.95 –1.02); 0.43	0.92 (0.86 –0.98); 0.0060
<i>Enterobacter cloacae</i>	26 (4)	15 (4)	0.9996 (0.99 –1.01); 0.93	1.03 (0.96 –1.1); 0.40
Gram-positive bacteria	253 (41)	140 (36)	1.01 (0.99 –1.02); 0.33	0.97 (0.93 –1.02); 0.22
MSSA	45 (7)	16 (4)	1.02 (0.97 –1.1); 0.46	0.98 (0.93 –1.02); 0.33
MRSA	49 (8)	30 (8)	1.02 (0.98 –1.1); 0.36	1.003 (0.92 –1.1); 0.95
CNS	2 (0)	3 (1)	1.1 (0.95 –1.3); 0.18	1.1 (0.88 –1.5); 0.32
<i>Enterococcus faecalis</i>	34 (6)	20 (5)	0.998 (0.99 –1.004); 0.43	0.9994 (0.93 –1.1); 0.99
<i>Enterococcus faecium</i>	12 (2)	4 (1)	0.998 (0.99 –1.01); 0.61	1.1 (0.93 –1.3); 0.29
VRE ^d	39 (6)	17 (4)	1.01 (0.99 –1.03); 0.59	0.90 (0.82 –0.98); 0.015
<i>Streptococcus</i> spp.	34 (6)	22 (6)	1.003 (0.99 –1.02); 0.71	1.1 (0.95 –1.2); 0.30
Anaerobic bacteria	65 (11)	39 (10)	0.996 (0.96 –1.03); 0.81	1.03 (0.97 –1.1); 0.33
<i>Clostridium difficile</i>	33 (5)	15 (4)	0.996 (0.99 –1.002); 0.21	1.1 (0.9994–1.2); 0.052

^aTo accommodate a correlated data structure corresponding to multiple episodes of infection per individual, the analysis of obesity¹ and nephrotoxicity² among episodes of infection was computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber-White “sandwich variance” estimates).

^c1.0 Referent is taken to be the absence of the variable being analyzed.

^dVariables included in the multivariable analysis.

CI = confidence interval; CNS = coagulase-negative staphylococci; MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *S. aureus*; RR = relative risk; VRE = vancomycin-resistant enterococci.

vancomycin dosing protocol (vancomycin 15 mg/kg intravenously [IV] every 8–12 h) with a revised dosing protocol (i.e., 10 mg/kg IV every 12 h or 15 mg/kg every 24 h) in a cohort of 138 obese patients [29]. The authors concluded that the revised protocol improved the attainment of target trough concentrations with minimal nephrotoxicity compared with the original protocol. However, the timing of the first vancomycin trough measurement was not standardized in relation to the first vancomycin dose, and because of the low incidence of observed nephrotoxicity (i.e., four cases), alternative risk factors for nephrotoxicity could not be evaluated. Additionally, the revised protocol was associated with a significantly greater frequency of below-target trough concentrations than the original protocol. Lodise et al. retrospectively compared a standard vancomycin dose (i.e., <4 g/day), high vancomycin dose (i.e., ≥4 g/day), and linezolid in a series of 246 patients [33]. Those authors concluded that patients weighing more than 101.4 kg, patients taking ≥4 g/day of vancomycin, patients residing in the ICU, and patients with estimated creatinine clearance ≤86.6 mL/min had an independently greater nephrotoxicity rate, suggesting that a vancomycin ceiling exists. Although no difference was observed in the nephrotoxicity incidence in obese and lean patients using TBW and dosing at 15 mg/kg twice daily, our results may be explained by the fact that the vancomycin dose was capped at 1750–2000 mg twice daily. Thus, our patients never exceeded the 4 g/day threshold.

Recent strategies have begun to emerge regarding the role of antioxidants in the prevention of vancomycin-induced

nephrotoxicity [46,47]. Ocak et al. divided 30 rats into six groups (control, vancomycin, vancomycin and caffeic acid phenethyl ester, vancomycin and vitamin C, vancomycin and vitamin E, and vancomycin and N-acetylcysteine) and compared the consequent degree of nephrotoxicity [47]. On histopathologic analysis, vitamin E was the most successful at reducing vancomycin-induced tubular damage. However, vitamin C, N-acetylcysteine, and caffeic acid phenethyl ester also were protective.

Strengths and Limitations

Our study is strengthened by its large sample and multivariable analysis. However, this study may be limited by its retrospective design, which may have contributed to both recall and selection bias. Although we did adjust for potential confounders, it is possible that other, unforeseen confounders impacted our results. For example, use of nephrotoxic contrast media was not captured in our database. Additionally, we did not evaluate vancomycin loading doses; nephrotoxic medications outside of aminoglycosides, amphotericin B, or piperacillin-tazobactam; fluid status, vasopressor use, the role of capping vancomycin doses on outcomes or toxicity rates; or cumulative infectious exposure in close proximity and how this may have impacted the degree of nephrotoxicity. As previously mentioned, obesity may hasten the progression of renal insufficiency. Our database captured patients on admission for treatment of sepsis. Thus, the initial

TABLE 4. PATIENT OUTCOMES PER INFECTION EPISODE AFTER VANCOMYCIN TREATMENT STRATIFIED BY OBESITY

<i>Outcome</i>	<i>Lean n (%)</i>	<i>Obese n (%)</i>	<i>P[†]</i>
Number of patients	323 (61)	207 (39)	–
Number of infectious episodes	618 (61)	389 (39)	
HLOS (days)			
Mean $\pm$ SD	24 $\pm$ 32	24 $\pm$ 25	0.64
Median (IQR)	15 (21)	16 (25)	
Duration of vancomycin (d)			
Mean $\pm$ SD	9.1 $\pm$ 9.6	8.4 $\pm$ 7.6	0.94
Median (IQR)	6.0 (6.0)	6.0 (6.0)	
Vancomycin trough (mcg/mL)			
Mean $\pm$ SD	18 $\pm$ 11	17 $\pm$ 10	0.80
Median (IQR)	16 (13)	17 (13)	
> 20	123 (21)	78 (21)	0.71
16–20	51 (9)	44 (12)	0.65
11–15	54 (9)	19 (5)	0.84
$\leq$ 10	369 (62)	223 (61)	1.0 ref
Max creat during tx (mg/dL)			
Mean $\pm$ SD	1.6 $\pm$ 1.2	1.6 $\pm$ 1.3	0.73
Median (IQR)	1.2 (1.1)	1.2 (0.9)	
Final creat after tx (mg/dL)			
Mean $\pm$ SD	1.2 $\pm$ 0.91	1.2 $\pm$ 0.85	0.36
Median (IQR)	0.90 (0.70)	1.0 (0.50)	
Change in creat (max – initial) (mg/dL)			
Mean $\pm$ SD	0.30 $\pm$ 0.53	0.29 $\pm$ 0.56	0.59
Median (IQR)	0.10 (0.40)	0.10 (0.30)	
Change in creat (final – initial) (mg/dL)			
Mean $\pm$ SD	–0.072 $\pm$ 0.59	–0.10 $\pm$ 0.74	0.37
Median (IQR)	0.0 (0.30)	–0.10 (0.30)	
Lowest eGFR during tx (mL/min/1.73 m ²)			
> 60	310 (50)	190 (49)	1.0 ref
31–60	164 (27)	128 (33)	0.98
15–30	117 (19)	41 (11)	0.63
< 15	27 (4)	30 (8)	0.48
Final eGFR after tx (mL/min/1.73 m ²)			
> 60	419 (68)	250 (64)	1.0 ref
31–60	129 (21)	96 (25)	0.44
15–30	53 (9)	29 (7)	0.71
< 15	17 (3)	14 (4)	0.61
Nephrotoxicity			
No	475 (77)	319 (82)	1.0 ref
Yes	140 (23)	70 (18)	0.92
New-onset hemodialysis			
No	532 (86)	351 (90)	1.0 ref
Yes	84 (14)	37 (10)	0.45
Death			
No	531 (86)	331 (85)	1.0 ref
Yes	87 (14)	58 (15)	0.77

^aTo accommodate a correlated data structure corresponding to multiple episodes of infection per individual, the analysis of obesity among episodes of infection was computed using a generalized estimating equation (GEE) approach with robust standard errors (i.e., Huber-White “sandwich variance” estimates).

abx = antibiotics; creat = creatinine; eGFR = estimated glomerular filtration rate; HLOS = hospital length of stay; IQR = interquartile range; Max = maximum; SD = standard deviation; tx = treatment.

creatinine and eGFR values are representative of those obtained immediately prior to treatment with vancomycin. Unfortunately, our database did not capture the creatinine and eGFR values prior to the onset of critical illness. Patients were followed until death or hospital discharge, and thus, we were unable to define acute kidney injury using the Risk

Injury Failure Loss End-stage kidney disease (RIFLE) criteria for each patient given inadequate follow-up. Finally, external validity may be limited, given that this was a single-center study of septic surgical patients where a large percentage of infections are treated primarily by source control procedures rather than by antimicrobials alone.

Conclusion

No difference in nephrotoxicity was observed between lean and obese patients treated with vancomycin at our institution while using actual weight-based dosing capped at 2 g per dose given twice daily. Larger samples are needed to analyze this relation closely among “at-risk” subsets of this population. Additionally, future studies should be directed toward the evaluation of vancomycin loading doses; nephrotoxic medications beyond aminoglycosides, amphotericin B, and piperacillin-tazobactam; fluid status; vasopressor use; the role of capping vancomycin doses on outcomes or toxicity rates; and cumulative infectious exposure in close proximity and how these may have impacted the degree of nephrotoxicity.

Author Disclosure Statement

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