Top Guns: The “Maverick” and “Goose” of Empiric Therapy

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Abstract

Background: Vancomycin and piperacillin-tazobactam are commonly used first guns in the empiric management of critically ill patients. Current studies suggest an increased prevalence of acute kidney injury with concomitant use, however, these studies are few and limited by small sample size. The purpose of this study was to compare the prevalence of nephrotoxicity after treatment with vancomycin alone and concomitant vancomycin and piperacillin-tazobactam treatment at our institution.

Hypothesis: Concomitant vancomycin and piperacillin-tazobactam-treated patients will experience greater prevalence of nephrotoxicity compared with vancomycin-only treated patients.

Methods: This was a retrospective cohort of patients treated with vancomycin for gram-positive or mixed infections in our facility from 2005 to 2009 who were not receiving hemodialysis at the time of admission. Included patients were stratified by treatment with vancomycin, vancomycin/piperacillin-tazobactam, or vancomycin/an alternative gram-negative rod (GNR) antibiotic. p values for categorical variables were computed using χ^2 while continuous variables were computed using Kruskal-Wallis. Variables deemed statistically significant (< 0.05) were included in the multivariable, log-binomial regression model. Relative risk (RR) and 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.

Results: A total of 530 patients with 1,007 episodes of infection, were treated with vancomycin (150 patients/302 episodes of infection), vancomycin/piperacillin-tazobactam (213 patients/372 episodes of infection), or vancomycin/GNR alternative (167 patients/333 episodes of infection). Patient demographics, comorbidities, sites of infection, and organisms of infection were compared among groups. After adjusting for statistically significant variables, neither vancomycin/piperacillin-tazobactam (RR = 1.1, 95% CI = 0.99–1.2; $p = 0.073$) nor vancomycin/GNR alternative (RR = 1.1, 95% CI = 0.98–1.2; $p = 0.097$) were found to be associated with an increased risk for nephrotoxicity compared with vancomycin alone.

Conclusion: A difference in nephrotoxicity was not observed between vancomycin and vancomycin/piperacillin-tazobactam-treated patients at our institution. Concomitant use as empiric therapy is appropriate, although larger sample sizes are needed to analyze closely this relation among at-risk subsets of this population.

BROAD-SPECTRUM ANTIMICROBIAL THERAPY administered within the first hour of sepsis is one of the many recommendations highlighted by the Surviving Sepsis Campaign for the treatment of sepsis [1]. This spectrum of activity should take into consideration patient history, comorbidities, and drug allergies and local pathogens, but also cover the most common pathogens responsible for sepsis in hospitalized patients (i.e., gram-positive and gram-negative bacteria). Given the increase

of multi-drug-resistant pathogens (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-intermediate *S. aureus* [VISA], and *Pseudomonas aeruginosa*), vancomycin and piperacillin-tazobactam are used commonly as empiric treatment agents [1–5].

Previous studies reporting an association between vancomycin and nephrotoxicity have been conflicting [6–20]. By contrast, piperacillin-tazobactam has rarely been associated

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with nephrotoxicity [21]. More recently, an increased incidence of nephrotoxicity has been associated with the combined use of vancomycin and piperacillin-tazobactam compared with vancomycin alone [21,22]. However, these studies are few and limited by small sample size.

Thus, the purpose of this study was to compare the prevalence of nephrotoxicity after treatment with vancomycin alone, and concomitant vancomycin and piperacillin-tazobactam treatment at our institution. We hypothesized that concomitant vancomycin and piperacillin-tazobactam-treated patients will experience a greater prevalence of nephrotoxicity compared with vancomycin-only treated patients or patients treated with vancomycin and an alternative gram-negative agent.

Patients and Methods

Study design

Institutional Review Board approval was obtained prior to data analysis. Details of the database and methodology have been described previously and are summarized below [20]. This was a retrospective analysis of a prospectively maintained database of all adult surgical patients (i.e., general, abdominal organ transplant, and trauma) admitted to a level I trauma and tertiary care center from 1996 to 2012 and treated for sepsis. We queried the database for all patients treated with vancomycin from December 6, 2005 to December 4, 2009; data collection was complete for this time period. Patients receiving hemodialysis prior to vancomycin initiation were excluded. Included patients were then stratified by treatment with vancomycin alone, vancomycin/piperacillin-tazobactam, or vancomycin/an alternative gram-negative rod (GNR) antibiotic (i.e., ceftriaxone, cefepime, ceftazidime, ticarcillin-clavulanate, imipenem, meropenem, gentamicin, tobramycin, amikacin, aztreonam, ciprofloxacin, or levofloxacin). Demographics and comorbidities, sites of infection, organisms of infection, and outcomes were compared between groups.

Database

Patient data were collected prospectively every other day by electronic medical chart, 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. Site(s) of infection, antibiotic therapy and duration, and culture-determined organisms were recorded for each episode of infection.

Patients

Gender, age, race (patient-defined), solid organ transplant, trauma, obesity (body mass index [BMI] ≥ 30), diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, peripheral vascular disease, respiratory disease, ventilator dependence, renal insufficiency, initial creatinine, initial estimated glomerular filtration rate (eGFR), hepatic insufficiency, malignant disease, chronic steroid use, prior transfusion during same hospitalization, nosocomial infection, patient location at time of infection, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were evaluated at time of initial infectious episode. New onset or change in ventilator dependence, renal insufficiency, hyperlipidemia, transfusion, patient location, and APACHE II score were measured at the time of each subsequent infectious episode. Similarly, sites of

infection and organisms cultured were measured at time of each infectious episode. Outcomes evaluated included total number of infectious episodes treated per group, total number of antibiotics used per infectious episode and stratified by group, hospital length of stay, duration of vancomycin treatment per infectious episode, maximum vancomycin trough per infectious episode, maximum creatinine during vancomycin treatment per infectious episode, final creatinine after vancomycin treatment per infectious episode, change in creatinine 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 infectious episode, final eGFR after vancomycin treatment per infectious episode, nephrotoxicity per infectious episode, new onset hemodialysis during vancomycin treatment, and death. Patients were followed until death or hospital discharge.

Setting

As previously stated, the University of Virginia Health System is a level I trauma and tertiary care center. Our pharmacy department doses vancomycin based on total body weight (15 mg/kg every 12 h for normal renal function) and estimated renal function. However, the total initial empiric dose is capped at 1,750–2,000 mg per dose. A trough is measured prior to the fourth dose and the regimen is adjusted to achieve a trough of 10–20 mcg/mL (10–15 mcg/mL for less severe infections and 15–20 mcg/mL for MRSA, osteomyelitis, endocarditis, meningitis, sepsis, etc.).

Our pharmacy department doses piperacillin-tazobactam based on renal function and severity of infection. For normal renal function (creatinine clearance >40 mL/min), standard dosing is 3.375 g intravenously every 6 h infused over 30 min for uncomplicated infections or 4.5 g intravenously every 6 h to 8 h (maximum: 18 g daily) for complicated infections (i.e., nosocomial pneumonia, or intra-abdominal or surgical site infection with *P. aeruginosa*). For patients with creatinine clearances from 20–40 mL/min, dosing is 2.25 g every 6 h (3.375 g every 6 h for nosocomial pneumonia). For patients with creatinine clearances <20 mL/min, dosing is 2.25 g every 8 h (2.25 g every 6 h for nosocomial pneumonia).

Definitions

Infection criteria were defined according to the U.S. Centers for Disease Control and Prevention (CDC) [23]. Solid organ transplant was defined as kidney, liver, pancreas, heart, lung, kidney/pancreas, liver/pancreas, and small bowel. Pulmonary disease was defined as active treatment for lung disease prior to hospital admission. Renal insufficiency was defined as a serum creatinine ≥ 2.0 mg/dL at time of infection episode but without need for dialysis. Patient location at time of infection episode was defined as home, hospital ward, intensive care unit (ICU), or other. Initial creatinine and eGFR were recorded immediately prior to vancomycin initiation per infectious episode. Other comorbidities were defined by chart documentation, medication history, and/or patient examination. Vancomycin trough levels were defined as the greatest trough level documented in the patient's chart during the treatment period. Nephrotoxicity was defined as a 0.5 mg/dL increase in serum creatinine, a 50% increase in baseline serum creatinine, or a 50% decrease in baseline

TABLE 1. DEMOGRAPHICS AND COMORBIDITIES^a STRATIFIED BY VANCOMYCIN
VERSUS VANCCOMYCIN/GRAM-NEGATIVE ROD ANTIBIOTIC (EXCLUDING PIPERACILLIN-TAZOBACTAM)
VERSUS VANCOMYCIN/PIPERACILLIN-TAZOBACTAM

<i>Demographics/comorbidities</i>	<i>Vanc n (%)</i>	<i>Vanc/GNR n (%)</i>	<i>Vanc/P-T n (%)</i>	<i>p^b</i>	<i>RR (95% CI); p^c (nephrotoxicity)</i>	
Number of patients	150 (28)	167 (32)	213 (40)	—	—	
Number of infectious episodes	302 (30)	333 (33)	372 (37)	—	—	
Gender						
Female	93 (31)	147 (44)	138 (37)	0.0024	0.98	(0.93–1.03); 0.36
Age (years)						
Mean ± SD	58 ± 15	55 ± 17	53 ± 15	0.0005		
Median (IQR)	58 (22)	53 (22)	53 (20)			
Q1 (≤45)	60 (20)	101 (30)	98 (26)	0.0008	1.0 ref	
Q2 (46–55)	72 (24)	79 (24)	108 (29)		1.03	(0.95–1.1); 0.52
Q3 (56–67)	76 (25)	73 (22)	99 (27)		1.04	(0.96–1.1); 0.34
Q4 (>67)	94 (31)	80 (24)	67 (18)		1.01	(0.93–1.1); 0.83
Race						
White	265 (88)	289 (87)	316 (85)	—	1.0 ref	
Black	35 (12)	36 (11)	50 (13)		0.95	(0.85–1.1); 0.36
Other	2 (1)	2 (1)	2 (1)		1.2	(0.92–1.6); 0.18
Hispanic	0 (0)	6 (2)	4 (1)		1.1	(0.91–1.4); 0.27
Transplant ^d						
Yes	58 (19)	67 (20)	64 (17)	0.60	1.1	(0.98–1.1); 0.13
Trauma						
Yes	31 (12)	64 (20)	35 (10)	0.0010	0.94	(0.85–1.03); 0.20
Obesity						
BMI ≥30	118 (39)	129 (39)	142 (38)	0.97	0.99	(0.93–1.04); 0.62
Diabetes mellitus						
Yes	68 (23)	74 (22)	90 (24)	0.80	1.04	(0.93–1.2); 0.49
Hypertension						
Yes	114 (38)	129 (39)	145 (39)	0.94	1.1	(0.99–1.1); 0.13
Hyperlipidemia						
Yes	48 (16)	46 (14)	50 (13)	0.63	1.03	(0.94–1.1); 0.55
Cardiovascular disease						
Yes	101 (33)	75 (23)	78 (21)	0.0004	1.001	(0.94–1.1); 0.98
PVD						
Yes	14 (5)	20 (6)	12 (3)	0.21	1.1	(0.91–1.2); 0.51
Pulmonary disease						
Yes	41 (14)	45 (14)	61 (16)	0.46	0.98	(0.90–1.1); 0.72
Ventilator dependence						
Yes	86 (28)	105 (32)	54 (15)	<0.0001	0.95	(0.86–1.05); 0.32
Renal insufficiency						
Yes	34 (11)	18 (5)	17 (5)	0.0013	0.96	(0.82–1.1); 0.61
Initial creatinine						
Mean ± SD	1.3 ± 0.90	1.3 ± 0.95	1.3 ± 1.02	0.74		
Median (IQR)	0.95 (0.70)	1.0 (0.70)	1.0 (0.60)			
(≤1.0)	173 (57)	174 (52)	199 (53)	0.0013	1.0 ref	
(1.1–1.5)	54 (18)	77 (23)	93 (25)		0.99	(0.89–1.1); 0.78
(1.6–2.0)	19 (6)	46 (14)	35 (9)		0.998	(0.94–1.2); 0.98
(>2.0)	56 (19)	36 (11)	45 (12)		1.02	(0.89–1.2); 0.79
Initial eGFR						
(>60)	190 (63)	195 (59)	239 (64)	0.0503	1.0 ref	
(31–60)	72 (24)	90 (27)	87 (23)		0.97	(0.88–1.1); 0.61
(15–30)	37 (12)	35 (11)	29 (8)		1.1	(0.94–1.2); 0.30
(<15)	3 (1)	13 (4)	17 (5)		0.93	(0.72–1.2); 0.59
Hepatic insufficiency						
Yes	18 (6)	13 (4)	24 (6)	0.30	1.1	(0.88–1.3); 0.44

(continued)

TABLE 1 (CONTINUED)

Demographics/comorbidities	Vanc n (%)	Vanc/GNR n (%)	Vanc/P-T n (%)	p ^b	RR (95% CI); p ^c (nephrotoxicity)
Malignant disease					
Yes	43 (14)	45 (14)	36 (10)	0.14	0.93 (0.80–1.1); 0.37
Long-term steroid use					
Yes	71 (24)	83 (25)	72 (19)	0.18	1.1 (0.99–1.2); 0.092
Prior transfusion					
Yes	137 (45)	148 (44)	105 (28)	<0.0001	0.99 (0.94–1.1); 0.84
Nosocomial infection					
Yes	228 (76)	252 (76)	217 (58)	<0.0001	1.01 (0.92–1.1); 0.91
Patient location					
Home	72 (24)	81 (24)	155 (42)	<0.0001	1.0 ref
Hospital ward	91 (30)	78 (23)	107 (29)		1.003 (0.90–1.1); 0.96
ICU	116 (38)	143 (43)	92 (25)		0.999 (0.91–1.1); 0.99
Other	23 (8)	31 (9)	18 (5)		1.04 (0.92–1.2); 0.54
APACHE II Score					
Mean $\pm$ SD	17 $\pm$ 8	18 $\pm$ 8	15 $\pm$ 7	<0.0001	
Median (IQR)	17 (12)	18 (10)	15 (10)		
Q1 ($\leq$ 11)	77 (26)	67 (20)	138 (37)		1.0 ref
Q2 (12–16)	66 (22)	74 (22)	88 (24)		0.96 (0.85–1.1); 0.50
Q3 (17–21)	71 (24)	92 (28)	86 (23)		0.96 (0.86–1.1); 0.50
Q4 ($>$ 21)	88 (29)	100 (30)	60 (16)		1.1 (1.006–1.2); 0.039

^aVariables analyzed per infectious episode.

^bChi square and Kruskal-Wallis testing were used to compare demographics and comorbidities between groups.

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

^dTransplants included: 24 kidney, 58 liver, two pancreas, nine kidney/pancreas, two liver/kidney, and one small bowel.

Vanc=vancomycin; GNR=gram-negative rod; P-T=piperacillin-tazobactam; RR=relative risk; CI=confidence interval; SD=standard deviation; IQR=interquartile range; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; BMI=body mass index; PVD=peripheral vascular disease; eGFR=estimated glomerular filtration rate; ICU=intensive care unit; APACHE II=Acute Physiology and Chronic Health Evaluation II.

creatinine clearance [9,10,13,24]. End points of antibiotic therapy included culture-proven resistance or insensitivity, adequate treatment duration as defined by unit guidelines and specific to 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]), and/or death. Uncomplicated blood stream infections involving *S. aureus* and a treatable focus were treated for 14 d after culture-proven clearance. Complicated blood stream infections involving *S. aureus* (e.g., infected endovascular grafts, endocardial vegetations) were treated for 4 wks to 6 wks after culture-proven clearance. Mortality was defined as any cause of death after infection diagnosis while hospitalized.

Statistical analysis

Demographics and comorbidities, infection sites, pathogenic organisms, and outcomes were compared between patients treated with vancomycin alone, vancomycin/piperacillin-tazobactam, or vancomycin/alternative GNR antibiotic. p values for categorical variables were computed using χ^2 whereas continuous variables were computed using Kruskal-Wallis. Additionally, relative risk (RR) and 95% confidence intervals (CI), and p values were computed predicting nephrotoxicity 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 [25,26]. Variables deemed statistically significant for either comparison between groups or nephrotoxicity association, among the demographics and comorbidities, infection sites, and infection-related organisms, were included in the multivariable, log-binomial regression model. Analysis was performed using SAS Version 9.3 (SAS Institute, Cary, NC) programming software. Statistical significance was defined as $p < 0.05$.

Results

A total of 530 patients with 1,007 episodes of infection were treated with vancomycin (150 patients/302 episodes of infection), vancomycin/piperacillin-tazobactam (213 patients/372 episodes of infection), or vancomycin/alternative GNR antibiotic (167 patients/333 episodes of infection). On average, each patient treated with vancomycin experienced 1.8 ± 1.2 episodes of infection, each patient treated with vancomycin/piperacillin-tazobactam experienced 1.7 ± 1.2 episodes of infection, and each patient treated with vancomycin/alternative GNR antibiotic experienced 1.9 ± 1.2 episodes of infection ($p=0.058$). Additionally, each patient treated with vancomycin was treated on average with 3.9 ± 1.6 antibiotics per infectious episode, each patient treated with vancomycin/piperacillin-tazobactam was treated with 3.2 ± 1.1 antibiotics

per infectious episode, and each patient treated with vancomycin/alternative GNR antibiotic was treated with 3.8 ± 1.4 antibiotics per infectious episode ($p < 0.0001$).

Demographics and comorbidities stratified by treatment arm (i.e., vancomycin, vancomycin/piperacillin-tazobactam, or vancomycin/alternative GNR antibiotic) are listed in Table 1. Additionally, each variable's association with nephrotoxicity has been provided. Females, age, trauma, cardiovascular disease, ventilator dependence, renal insufficiency, initial creatinine, prior blood transfusion during the same hospitalization, nosocomial infection, patient location at time of infection, and APACHE II score were different between groups. Additionally, APACHE II score was associated with nephrotoxicity.

Sites of infection stratified by treatment arm are listed in Table 2. Additionally, each variable's association with nephrotoxicity has been provided. Infections related to the peritoneum, colon, skin/soft tissue, wound, and blood stream were different between groups.

Culture-identified organisms stratified by treatment arm are listed in Table 3. Additionally, each variable's association

with nephrotoxicity has been provided. Gram-negative bacteria in general, *Serratia* spp., *P. aeruginosa*, and *Enterobacter cloacae* were significantly different between groups. Additionally, *P. aeruginosa* and vancomycin-resistant *Enterococcus* were associated with nephrotoxicity.

Patient outcomes stratified by treatment arm are listed in Table 4. Patients were treated with vancomycin for a similar duration across all groups. Although differences regarding eGFR were present during treatment with vancomycin across all groups, nephrotoxicity and new onset hemodialysis did not differ. Interestingly, hospital length of stay and incidence of death was longer and greater, respectively, within groups treated with vancomycin alone and vancomycin/alternative GNR antibiotic compared with the group treated with vancomycin/piperacillin-tazobactam.

Variables found to be different between groups and/or those found to be associated with nephrotoxicity (i.e., gender, age, trauma, cardiovascular disease, ventilator dependence, initial creatinine, prior transfusion, nosocomial infection, APACHE II score, peritoneal infections, colon infections, skin infections, surgical site infections, blood stream infections, *Serratia*

TABLE 2. SITES OF INFECTION^a STRATIFIED BY VANCOMYCIN VERSUS VANCOMYCIN/GRAM-NEGATIVE ROD ANTIBIOTIC (EXCLUDING PIPERACILLIN-TAZOBACTAM) VERSUS VANCOMYCIN/PIPERACILLIN-TAZOBACTAM

Sites	Vanc n (%)	Vanc/GNR n (%)	Vanc/P-T n (%)	p ^b	RR (95% CI); p ^c (nephrotoxicity)
Number of patients	150 (28)	167 (32)	213 (40)	—	—
Number of infectious episodes	302 (30)	333 (33)	372 (37)	—	—
CNS					
Yes	0 (0)	1 (0)	0 (0)	—	—
Peritoneum					
Yes	53 (18)	78 (23)	107 (29)	0.0030	0.996 (0.95–1.04); 0.87
Upper GI					
Yes	1 (0)	1 (0)	2 (1)	0.86	0.93 (0.77–1.1); 0.42
Colon					
Yes	31 (10)	12 (4)	6 (2)	<0.0001	1.1 (0.998–1.2); 0.058
Lung					
Yes	76 (25)	80 (24)	68 (18)	0.065	0.997 (0.96–1.04); 0.89
Pleura					
Yes	2 (1)	4 (1)	3 (1)	0.75	0.90 (0.73–1.1); 0.30
Skin/soft tissue					
Yes	16 (5)	19 (6)	36 (10)	0.044	0.96 (0.89–1.03); 0.25
Wound					
Yes	18 (6)	38 (11)	54 (15)	0.0018	0.9997 (0.95–1.1); 0.99
Line					
Yes	11 (4)	10 (3)	11 (3)	0.86	1.03 (0.95–1.1); 0.47
Blood					
Yes	59 (20)	52 (16)	46 (12)	0.039	0.98 (0.94–1.009); 0.16
Urine					
Yes	34 (11)	36 (11)	37 (10)	0.85	1.02 (0.99–1.1); 0.23

^aVariables analyzed per infectious episode.

^bChi square was used to compare sites of infection between groups.

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

Vanc = vancomycin; GNR = gram-negative rod; P-T = piperacillin-tazobactam; RR = relative risk; CI = confidence interval; CNS = central nervous system; GI = gastrointestinal.

TABLE 3. ORGANISMS^a STRATIFIED BY VANCOMYCIN VERSUS VANCOMYCIN/GRAM-NEGATIVE ROD ANTIBIOTIC (EXCLUDING PIPERACILLIN-TAZOBACTAM) VERSUS VANCOMYCIN/PIPERACILLIN-TAZOBACTAM

Organism	Vanc n (%)	Vanc/GNR n (%)	Vanc/P-T n (%)	p ^b	RR (95% CI); p ^c (nephrotoxicity)
Number of patients	150 (28)	167 (32)	213 (40)	—	—
Number of infectious episodes	302 (30)	333 (33)	372 (37)	—	—
Fungal	46 (15)	51 (15)	53 (14)	0.91	0.98 (0.92–1.05); 0.56
<i>Candida albicans</i>	15 (5)	21 (6)	25 (7)	0.62	0.94 (0.86–1.03); 0.19
<i>Candida glabrata</i>	18 (6)	14 (4)	20 (5)	0.59	1.04 (0.95–1.1); 0.42
Gram-negative bacteria	142 (47)	117 (35)	104 (28)	<0.0001	0.99 (0.94–1.05); 0.81
<i>Escherichia coli</i>	32 (11)	33 (10)	33 (9)	0.75	0.94 (0.88–1.01); 0.076
<i>Klebsiella pneumonia</i>	26 (9)	18 (5)	22 (6)	0.22	1.01 (0.90–1.1); 0.92
<i>Serratia</i> spp.	10 (3)	2 (1)	3 (1)	0.0074	1.02 (0.72–1.4); 0.92
<i>Pseudomonas aeruginosa</i>	34 (11)	11 (3)	10 (3)	<0.0001	0.92 (0.86–0.98); 0.0060
<i>Enterobacter cloacae</i>	21 (7)	12 (4)	8 (2)	0.0063	1.03 (0.96–1.1); 0.40
Gram-positive bacteria	112 (37)	123 (37)	158 (42)	0.23	0.97 (0.93–1.02); 0.22
MSSA	19 (6)	22 (7)	20 (5)	0.78	0.98 (0.93–1.02); 0.33
MRSA	23 (8)	28 (8)	28 (8)	0.90	1.003 (0.92–1.1); 0.95
CNS	2 (1)	1 (0)	2 (1)	0.80	1.1 (0.88–1.5); 0.32
<i>Enterococcus faecalis</i>	11 (4)	23 (7)	20 (5)	0.19	0.9994 (0.93–1.1); 0.99
<i>Enterococcus faecium</i>	6 (2)	5 (2)	5 (1)	0.79	1.1 (0.93–1.3); 0.29
VRE	12 (4)	16 (5)	28 (8)	0.10	0.90 (0.82–0.98); 0.015
<i>Streptococcus</i> spp.	15 (5)	13 (4)	28 (8)	0.096	1.1 (0.95–1.2); 0.30
Anaerobic bacteria	38 (13)	35 (11)	31 (8)	0.20	1.03 (0.97–1.1); 0.33

^aVariables analyzed per infectious episode.

^bChi square was used to compare organisms between groups.

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

Vanc=vancomycin; GNR=gram-negative rod; P-T=piperacillin-tazobactam; RR=relative risk; CI=confidence interval; MSSA=methicillin-sensitive *Staphylococcus aureus*; MRSA=methicillin-resistant *Staphylococcus aureus*; CNS=coagulase negative staphylococcus; VRE=vancomycin-resistant enterococcus.

spp. infections, *P. aeruginosa* infections, *E. cloacae* infections, and vancomycin-resistant enterococcus) were included in the multivariable, log-binomial regression model listed in Table 5. APACHE II score >21 (RR=1.1, 95% CI=1.01–1.3; p=0.032) was found to be associated independently with increased nephrotoxic risk. Neither patients treated with vancomycin and piperacillin-tazobactam (RR=1.1, 95% CI=0.99–1.2; p=0.073) nor patients treated with vancomycin and alternative GNR antibiotic (RR=1.1, 95% CI=0.98–1.2; p=0.097) experienced an increase in nephrotoxic risk compared with patients treated with vancomycin alone.

Discussion

We present one of the largest cohorts evaluating concomitant vancomycin/piperacillin-tazobactam therapy and nephrotoxicity published to date [21,22,27]. Our study observed a 21% incidence of nephrotoxicity among all infectious episodes of adult surgical patients admitted from December 6, 2005 to December 4, 2009 and treated for sepsis at our institution using either vancomycin alone (22%), vancomycin/alternative GNR antibiotic (20%), or vancomycin/piperacillin-tazobactam (21%). Additionally, we observed a 12% incidence of new-onset hemodialysis; vancomycin alone (9%), vancomycin/alternative GNR antibiotic (11%), or vancomycin/piperacillin-tazobactam (7%). Using multivariable analysis, treatment with vancomycin/alternative GNR antibiotic and vancomycin/piperacillin-tazobactam

were not observed to be associated with nephrotoxicity compared with treatment with vancomycin alone.

Vancomycin is a bactericidal glycopeptide [28]. Its mechanism of action involves the inhibition of peptidoglycan and cell wall growth of gram-positive organisms. Elimination is primarily by the kidneys and vancomycin-associated nephrotoxicity is theorized to occur at the proximal renal tubule as a result of oxidative stress and free radical generation [9,13]. To minimize the incidence of vancomycin-associated nephrotoxicity, current practice guidelines recommend treatment dosages of 15–20 mg/kg every eight to 12 h in patients with normal renal function [29]. This serves to maximize the frequency of troughs between 10–20 mg/L. A previous study of ours comparing incidence of nephrotoxicity between septic, critically ill patients treated with either vancomycin (298 patients/571 episodes of infection) or linezolid (247 patients/475 episodes of infection) observed a similar nephrotoxic profile when treated within the 10–20 mg/L range [20].

Piperacillin-tazobactam is a bactericidal, β -lactam combined with a β -lactamase inhibitor [30]. Its mechanism of action involves the inhibition of cell wall growth of gram-positive and gram-negative organisms. Bacteria may develop resistance to β -lactams by synthesizing β -lactamase, which serves to decouple the β -lactam ring structure. However, the combined use of a β -lactamase inhibitor competitively binds the β -lactamase, thus preventing this decoupling action. Elimination is primarily by the kidneys

TABLE 4. PATIENT OUTCOMES AFTER VANCOMYCIN TREATMENT STRATIFIED BY VANCOMYCIN VERSUS VANCOMYCIN/GRAM-NEGATIVE ROD ANTIBIOTIC (EXCLUDING PIPERACILLIN-TAZOBACTAM) VERSUS VANCOMYCIN/PIPERACILLIN-TAZOBACTAM

Outcome	Vanc n (%)	Vanc/GNR n (%)	Vanc/P-T n (%)	p ^a
Number of patients	150 (28)	167 (32)	213 (40)	—
Number of infectious episodes	302 (30)	333 (33)	372 (37)	
HLOS (days) ^b				
Mean $\pm$ SD	25 $\pm$ 27	27 $\pm$ 35	21 $\pm$ 26	0.0015
Median (IQR)	15 (28)	18 (22)	12 (18)	
Duration of vancomycin (days) ^c				
Mean $\pm$ SD	8.9 $\pm$ 8.8	9.3 $\pm$ 9.8	8.3 $\pm$ 8.04	0.23
Median (IQR)	6 (6)	7 (6)	6 (5)	
Vancomycin trough ^b				
Mean $\pm$ SD	15 $\pm$ 8.6	16 $\pm$ 11	17 $\pm$ 12	0.49
Median (IQR)	15 (13)	13 (12)	15 (15)	
(>20)	22 (15)	28 (18)	49 (24)	0.0085
(16–20)	16 (11)	12 (8)	13 (6)	
(11–15)	8 (6)	23 (15)	12 (6)	
($\leq$ 10)	97 (68)	91 (59)	129 (64)	
Maximum creatinine during Tx ^c				
Mean $\pm$ SD	1.6 $\pm$ 1.2	1.5 $\pm$ 1.1	1.6 $\pm$ 1.2	0.98
Median (IQR)	1.2 (1.3)	1.2 (0.9)	1.2 (0.9)	
Final creatinine after Tx ^c				
Mean $\pm$ SD	1.2 $\pm$ 0.83	1.2 $\pm$ 1.04	1.2 $\pm$ 0.77	0.048
Median (IQR)	1.0 (0.70)	0.90 (0.60)	1.0 (0.50)	
Change in creatinine (maximum-initial) ^c				
Mean $\pm$ SD	0.34 $\pm$ 0.60	0.27 $\pm$ 0.52	0.29 $\pm$ 0.52	0.57
Median (IQR)	0.10 (0.40)	0.10 (0.30)	0.10 (0.30)	
Change in creatinine (final-initial) ^c				
Mean $\pm$ SD	−0.075 $\pm$ 0.58	−0.072 $\pm$ 0.58	−0.10 $\pm$ 0.76	0.055
Median (IQR)	0.0 (0.30)	−0.10 (0.40)	0.0 (0.30)	
Lowest eGFR during Tx ^c				
(>60)	147 (49)	160 (48)	193 (52)	0.012
(31–60)	84 (28)	92 (28)	116 (31)	
(15–30)	60 (20)	60 (18)	38 (10)	
(<15)	11 (4)	21 (6)	25 (7)	
Final eGFR after Tx ^c				
(>60)	204 (68)	216 (65)	249 (67)	0.0076
(31–60)	66 (22)	66 (20)	93 (25)	
(15–30)	28 (9)	32 (10)	22 (6)	
(<15)	4 (1)	19 (6)	8 (2)	
Nephrotoxicity ^c				
Yes	66 (22)	68 (20)	76 (21)	0.89
New-onset hemodialysis ^b				
Yes	13 (9)	19 (11)	14 (7)	0.25
Death ^b				
Yes	21 (14)	23 (14)	14 (7)	0.030

^aChi square and Kruskal-Wallis testing were used to compare patient outcomes between groups.

^bVariables analyzed per patient.

^cVariables analyzed per infectious episode.

Vanc = vancomycin; GNR = gram-negative rod; P-T = piperacillin-tazobactam; HLOS = hospital length of stay; SD = standard deviation; IQR = interquartile range; Tx = treatment; eGFR = estimated glomerular filtration rate.

and piperacillin-tazobactam-associated nephrotoxicity has rarely been cited in the literature (<1%) [21,31,32]. Case reports of this are largely based on temporal dosing, and a definitive association has not been delineated. Additionally, all of these reports involve patients with oncologic diagnoses who were experienced dehydration, critical illness, sepsis, and/or other nephrotoxic exposure. Current practice guidelines recommend treatment dosages of 3.375 g every

6 h, 4.5 g every eight hours, or 4.5 g every 6 h infused over a 30-min duration [30].

As the incidence of multi-drug-resistant pathogens continues to increase, patients are managed commonly using combination therapy. One example of this is the treatment of MRSA and VISA using combined vancomycin/piperacillin-tazobactam. Dilworth et al. [27] conducted an in vitro study to evaluate whether vancomycin/piperacillin-tazobactam

TABLE 5. MULTIVARIABLE ANALYSIS
PREDICTING NEPHROTOXICITY^a

Variables	RR (95% CI); p ^b		
Vanc	1.0 ref		
Vanc/GNR	1.1	(0.98–1.2);	0.097
Vanc/P-T	1.1	(0.99–1.2);	0.073
Gender	1.0 ref		
Male			
Female	0.97	(0.92–1.04);	0.41
Age	1.0 ref		
Q1 (≤45)			
Q2 (46–55)	1.02	(0.91–1.1);	0.75
Q3 (56–67)	1.02	(0.93–1.1);	0.66
Q4 (>67)	0.98	(0.89–1.1);	0.67
Trauma	1.0 ref		
No			
Yes	0.94	(0.80–1.1);	0.48
Cardiovascular disease	1.0 ref		
No			
Yes	0.99	(0.92–1.1);	0.71
Ventilator dependence	1.0 ref		
No			
Yes	0.90	(0.78–1.03);	0.12
Initial creatinine	1.0 ref		
(≤1.0)			
(1.1–1.5)	0.93	(0.83–1.04);	0.202
(1.6–2.0)	0.91	(0.76–1.1);	0.31
(>2.0)	0.92	(0.79–1.1);	0.31
Prior transfusion	1.0 ref		
No			
Yes	1.04	(0.96–1.1);	0.31
Nosocomial infection	1.0 ref		
No			
Yes	1.003	(0.91–1.1);	0.94
APACHE II score	1.0 ref		
Q1 (≤11)			
Q2 (12–16)	0.97	(0.86–1.1);	0.603
Q3 (17–21)	0.98	(0.86–1.1);	0.76
Q4 (>21)	1.2	(1.01–1.3);	0.032
Peritoneum	1.0 ref		
No			
Yes	0.96	(0.91–1.02);	0.20
Colon	1.0 ref		
No			
Yes	1.1	(1.001–1.2);	0.047
Skin	1.0 ref		
No			
Yes	0.93	(0.86–1.001);	0.053
Wound	1.0 ref		
No			
Yes	0.98	(0.93–1.03);	0.39
Blood	1.0 ref		
No			
Yes	0.97	(0.93–1.008);	0.11
<i>Serratia</i> spp.	1.0 ref		
No			
Yes	1.1	(0.80–1.6);	0.49
<i>Pseudomonas aeruginosa</i>	1.0 ref		
No			
Yes	0.96	(0.90–1.02);	0.19

(continued)

TABLE 5 (CONTINUED)

Variables	RR (95% CI); p ^b		
<i>Enterobacter cloacae</i>	1.0 ref		
No			
Yes	1.06	(0.96–1.2);	0.27
VRE	1.0 ref		
No			
Yes	0.87	(0.80–0.96);	0.0033

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

RR=relative risk; CI=confidence interval; Vanc=vancomycin; GNR=gram-negative rod; P-T=piperacillin-tazobactam; Q1=first quartile; Q2=second quartile; Q3=third quartile; Q4=fourth quartile; APACHE II=Acute Physiology and Chronic Health Evaluation II; VRE=vancomycin-resistant enterococcus.

were synergistic against MRSA and VISA. The authors observed an increased antimicrobial activity using sub-inhibitory concentrations of vancomycin when combination therapy was used. However, this synergistic benefit may not be without cost.

Recent studies have begun to evaluate the incidence of nephrotoxicity associated with combination therapy compared with vancomycin treatment alone as this may impact empiric antimicrobial therapy; however, these are few and the results are conflicting [21,22,33]. Burgess et al. [21] conducted a single-center, retrospective cohort study comparing incidence of nephrotoxicity among patients treated with vancomycin for 48 h (n=99, 8.1% nephrotoxicity incidence) and patients treated with vancomycin/piperacillin-tazobactam for 48 h (n=92, 16.3% nephrotoxicity incidence) [21]. Using multivariable analysis, the authors observed a significantly greater association between combination therapy and nephrotoxicity (odds ratio=2.48; p=0.032) compared with monotherapy with vancomycin. Similarly, Gomes et al. [22] conducted a retrospective matched cohort study comparing nephrotoxicity incidence among patients treated for 48 h with vancomycin/piperacillin-tazobactam (n=112, 34.8% nephrotoxicity incidence) to vancomycin/cefepime (n=112, 12.5% nephrotoxicity incidence). Using multivariable analysis, the authors observed that combination therapy with vancomycin/piperacillin-tazobactam had a significantly increased association with nephrotoxicity compared with treatment with vancomycin/cefepime (odds ratio=5.67, 95% CI=1.66–19.33). By contrast, Moenster et al. [33] conducted a retrospective cohort study comparing incidence of nephrotoxicity among patients with diabetes mellitus with osteomyelitis treated for 72 h with either vancomycin/piperacillin-tazobactam (n=109, 29.3% nephrotoxicity incidence) or vancomycin/cefepime (n=30, 13.3% nephrotoxicity incidence). Using multivariable analysis, the authors did not observe an increased association between nephrotoxicity and vancomycin/piperacillin-tazobactam therapy compared with vancomycin/cefepime (odds ratio=3.45, 95% CI=0.96–12.4; p=0.057). Rather, greater weight and vancomycin troughs were associated with a significantly increased risk of nephrotoxicity.

One explanation for a possible association between combination therapy and nephrotoxicity may be related to drug elimination inhibition. Jensen et al. [34] conducted a randomized control trial evaluating kidney failure in critically ill patients treated with broad-spectrum antibiotics. A multiple effects model comparing the eGFR of all patients showed that patients with existing renal dysfunction experienced delayed renal recovery when treated with piperacillin-tazobactam compared with other commonly administered antibiotics (i.e., meropenem, cefuroxime, ciprofloxacin, and vancomycin).

Interestingly, when piperacillin-tazobactam was discontinued, renal dysfunction improved more rapidly than patients treated with the other antibiotic protocols. This delay in recovery could negatively impact the elimination of vancomycin, thus resulting in greater than normal trough levels further compounding the acute kidney injury.

Strengths and Weaknesses

Our study is strengthened by its large sample size and use of multivariable analysis, however, it may be limited by its retrospective design. This may have contributed to both recall and selection bias. Whereas we did adjust for potential confounders, unforeseen confounders exist and may have impacted our results. For example, baseline creatinine and eGFR values prior to the onset of critical illness, use of nephrotoxic contrast dyes, or medications other than those mentioned previously, vancomycin-loading doses, vasopressor use, or fluid status was not captured within our database. Additionally, we did not evaluate the role of capping vancomycin doses on nephrotoxicity, or the impact of cumulative infectious exposure on nephrotoxicity. Patients were followed until death or hospital discharge, and thus, we were unable to define acute kidney injury using Risk Injury Failure Loss End (RIFLE) stage kidney disease criteria for each patient because of inadequate follow-up. Finally, external validity may be limited given that this was a single-center study of surgical patients with sepsis where a large percentage of infections are treated primarily by source control procedures versus antimicrobial agents alone.

Conclusion

No difference in nephrotoxicity was observed between vancomycin and vancomycin/piperacillin-tazobactam-treated patients at our institution. Concomitant use as empiric therapy is appropriate, although larger sample sizes are needed to analyze this relationship among at-risk subsets of this population.

Author Disclosure Statement

The authors declare no conflicts of interest.

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