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MAJOR ARTICLE

Risk of Acute Kidney Injury in Patients on Concomitant Vancomycin and Piperacillin–Tazobactam Compared to Those on Vancomycin and Cefepime

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Background. Recent evidence suggests that among patients receiving vancomycin, receipt of concomitant piperacillin–tazobactam increases the risk of nephrotoxicity. Well-controlled, adequately powered studies comparing rates of acute kidney injury (AKI) among patients receiving vancomycin + piperacillin–tazobactam (VPT) compared to similar patients receiving vancomycin + cefepime (VC) are lacking. In this study we compared the incidence of AKI among patients receiving combination therapy with VPT to a matched group receiving VC.

Methods. A retrospective, matched, cohort study was performed. Patients were eligible if they received combination therapy for ≥48 hours. Patients were excluded if their baseline serum creatinine was >1.2mg/dL or they were receiving renal replacement therapy. Patients receiving VC were matched to patients receiving VPT based on severity of illness, intensive care unit status, duration of combination therapy, vancomycin dose, and number of concomitant nephrotoxins. The primary outcome was the incidence of AKI. Multivariate modeling was performed using Cox proportional hazards.

Results. A total of 558 patients were included. AKI rates were significantly higher in the VPT group than the VC group (81/279 [29%] vs 31/279 [11%]). In multivariate analysis, therapy with VPT was an independent predictor for AKI (hazard ratio = 4.27; 95% confidence interval, 2.73–6.68). Among patients who developed AKI, the median onset was more rapid in the VPT group compared to the VC group (3 vs 5 days P =< .0001).

Conclusion. The VPT combination was associated with both an increased AKI risk and a more rapid onset of AKI compared to the VC combination.

Keywords. vancomycin; piperacillin–tazobactam; cefepime; acute kidney injury; nephrotoxicity.

Empiric antimicrobial therapy for the treatment of healthcare-associated infections frequently includes coverage for both methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa.* Common regimens include vancomycin in combination with an antipseudomonal b-lactam [1]. Piperacillin–tazobactam and cefepime are among the most common agents used for empiric antipseudomonal coverage.

A hospital's selection of piperacillin–tazobactam vs cefepime as the "workhorse" antipseudomonal antibiotic has traditionally been based on institutional susceptibility trends, acquisition costs, and other formulary considerations. Concerns regarding nephrotoxicity have become increasingly prominent. While vancomycin has long been associated with acute kidney injury (AKI), recent evidence suggests that patients receiving combination therapy with piperacillin–tazobactam have a higher incidence of AKI compared to patients receiving vancomycin monotherapy [2] or those receiving combination therapy with vancomycin and cefepime (VC) [3].

However, the finding of increased toxicity in patients receiving vancomycin and piperacillin–tazobactam (VPT) combination therapy compared to VC has not been universal. A recent analysis showed no difference in AKI rates among intensive care unit (ICU) patients receiving either combination [4]. Prior studies have been limited by relatively small sample sizes, notable diversity in the patients receiving the different combination therapy regimens, and suboptimal study design.

In light of the conflicting results and methodological limitations of prior studies as well as the importance of clearly understanding whether or not combination therapy with VPT is associated with an increased AKI risk, this retrospective, matched, cohort study was designed to definitively address the

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following questions: is combination therapy with VPT associated with greater AKI risk compared to VC? If so, how much greater is the risk?

METHODS

Study Settings and Design

This was a retrospective, matched, cohort study that compared the incidence of AKI among patients on concomitant VC and those receiving VPT. The study was conducted at the Detroit Medical Center (DMC), a tertiary care health system in metropolitan Detroit, Michigan, comprised of 5 acute care hospitals with more than 2000 inpatient beds. The institutional review boards at the DMC and Wayne State University approved the study prior to initiation.

Study Population

The study population consisted of patients aged ≥18 years admitted to the DMC between 1 December 2011 and 31 December 2013. Patients included in the study received combination therapy with VC or VPT for ≥48 hours and had the 2 antibiotics initiated within 24 hours of one another. For patients who received combination therapy multiple times during hospitalization, only the initial regimen was included. Patients were excluded if the baseline serum creatinine was >1.2 mg/dL or they required renal replacement therapy at the time of initiation of combination therapy.

Patients were divided into 2 groups based on the combination regimen received. The patients in the VC group were matched to the VPT group on 5 variables associated with the development of AKI in a 1:1 ratio. The matching was performed based on severity of sepsis at the time that the combination antibiotics were started (dichotomized to presence or absence of severe sepsis/septic shock) [5], ICU status at onset of combination therapy, duration of combination therapy (divided into 3 categories: ≤3 days, 4–7 days, >7 days), the daily dose of vancomycin received (divided into 3 categories: < 2 grams/day, 2–4 grams/day, and >4 grams/day), and number of concomitant nephrotoxic agents received while on combination therapy.

Covariates Collected

Data abstracted from medical records included patient demographics; comorbidities, including Charlson comorbidity index [6]; severity of sepsis based on systemic inflammatory response syndrome criteria [5]; mechanical ventilation; infectious diagnosis; and receipt of concomitant nephrotoxins while receiving combination therapy. Antibiotic therapy variables collected included dose and duration of therapy. Vancomycin trough levels were also collected. Vancomycin loading dose was defined as an initial vancomycin dose that was higher than subsequent maintenance doses. The variables used for matching were extracted during the time period between 2 days prior and 2 days after initiation of combination therapy, with the highest values used for this purpose. Vasopressors, aminoglycosides, colistin, amphotericin B, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, diuretics, and intravenous contrast were considered as nephrotoxic agents.

Vancomycin Trough Value Assessment

In order to assess the impact of vancomycin exposures on development of AKI, the median trough of vancomycin prior to AKI was calculated. For patients who did not develop AKI, median vancomycin troughs during the entire duration of combination therapy were analyzed, whereas among patients who developed AKI, only trough values obtained before the onset of AKI were included. Patients in whom trough values were not obtained during therapy and those who did not have trough values obtained prior to the development of AKI were excluded from trough analyses.

Acute Kidney Injury Definitions

Determination of AKI was based on 3 definitions: According to the RIFLE (Risk, Injury, Failure, Loss, End Stage Renal Disease) criteria [7], the Acute Kindey Injury Network (AKIN) criteria [8], and vancomycin consensus guideline definition [9]. For RIFLE criteria, the terms *risk*, *injury*, and *failure* were defined as follows: risk, a rise in creatinine by 1.5 times baseline or a decrease in glomerular filtration rate (GFR) by 25%; injury, a rise in creatinine of 2 times baseline or a decrease in the GFR by 50%; and failure, a rise in creatinine by 3 times baseline or a GFR decrease by 75%. AKIN criteria were categorized into 3 stages: a rise in creatinine by 1.5-fold or 0.3 mg/dL was categorized as stage 1, a 2-fold rise in creatinine was categorized as stage 2, and a rise in creatinine by 3-fold or ≥ 4 mg/dL or initiation of renal replacement therapy was categorized as stage 3. For the vancomycin consensus guidelines, AKI was defined as a rise in baseline serum creatinine by ≥50% or >0.5 mg/dL sustained over at least 2 consecutive measurements ranging from the time of initiation until 72 hours post-completion of vancomycin therapy. RIFLE-defined AKI was used for all multivariate analyses, where meeting any stage of the RIFLE criteria was considered AKI.

Statistical Analyses

All statistical analyses were performed using SAS software, version 9.3 (Cary, North Carolina). Matched bivariate analyses comparing patients receiving VC to patients receiving VPT were conducted using conditional logistic regression modeling. For bivariate unmatched analysis, Fisher exact test and χ^2 test were used to analyze dichotomous variables, and Student *t* test and Wilcoxon rank-sum test were used for continuous variables.

To determine the impact of VPT on AKI risk in both bivariate and multivariate analyses, Cox proportional hazards methodology was used. In multivariate analysis to control for residual differences between the VPT and VC groups, all variables with a *P* value <.1 in the bivariate matched analysis comparing VPT and VC groups were included, along with treatment group (VPT vs

VC), in a multivariate model for AKI. In this model the event of interest was development of RIFLE-defined AKI. All *P* values were 2 sided and a *P* value <.05 was considered statistically significant. Crude rates of AKI of the 2 study groups were compared using a Kaplan–Meier curve and the log-rank test.

RESULTS

Baseline Characteristics

A total of 320 patients who received VPT and 803 patients who received VC during the study period were identified. Of the 320 VPT patients, adequate VC matches were identified for 279. Thus, 279 VPT–VC pairs were included in the final study population, for a total of 558 patients. The mean age was 55.9 ± 16.6 years. Patients in both VC and VPT groups had similar baseline characteristics in terms of age, length of ICU stay, Charlson comorbidity index score, baseline creatinine, and use of concomitant nephrotoxins (Table 1). There were more females in the VC group, and more patients were white in the VPT group. Patients were more likely to have had connective tissue disease and hypertension in the VC group compared to those in the VPT group. Patients in the VPT group had a higher incidence of septic shock and skin and soft tissue infections. Combination therapy with both VPT and VC was initiated as empiric therapy in all patients. There were no differences in the number of patients receiving vancomycin loading doses, the median loading or maintenance doses of vancomycin given, or the median vancomycin trough values between the 2 groups.

Comparative Rates of AKI in VC and VPT Patients

The rate of AKI was higher among patients receiving VPT compared to those receiving VC combination therapy. Based on RIFLE criteria, 81 patients in the VPT group developed AKI compared to 31 patients in the VC group (29.0% vs 11.1%; hazard ratio [HR] = 4.0; 95% confidence interval [CI], 2.6–6.2; *P* < .0001). Rates of AKI were also higher per AKIN criteria (32% in the VPT vs 14% in the VC group; HR = 3.5; 95% CI, 2.3–5.2; *P* < .0001) and per vancomycin consensus guidelines definition (24% in VPT vs 8.2% in VC; HR = 4.4; 95% CI, 2.7–7.3; *P* < .0001). In multivariate analysis, after controlling for residual differences between the VPT and VC groups (race, gender, admission from home, comorbid conditions, presence of septic shock, baseline serum white blood cell count, and source of infection), VPT was independently associated with RIFLE-defined AKI (HR = 4.3; 95% CI, 2.7–6.7; *P* < .0001).

Characterization of AKI

Of the patients who developed RIFLE-defined AKI (n = 31 in the VC group and n = 81 in the VPT group), the onset of AKI was more rapid in patients receiving VPT. The median duration of combination therapy prior to development of AKI was 5 days (interquartile range [IQR], 3–7 days) in the VC and 3 days (IQR, 2–5 days) in the VPT group; *P* < .0001. Survival curves depicting time to AKI in the 2 treatment groups were constructed (Figures 1 and 2) and demonstrate the increased incidence and more rapid onset of AKI among patients in the VPT group compared to those in the VC group (*P* < .0001). Importantly, the Kaplan–Meier curves also show that the daily rate of AKI among at-risk patients remained consistently higher in the VPT group compared to the VC group throughout the entire first week of combination therapy.

Other Outcome Variables

The median length of stay after initiation of combination therapy was longer for VPT patients compared to VC patients (8 days vs 6 days; *P* = .01). There was no difference in mortality between the 2 groups.

Impact of Vancomycin Troughs on AKI

Although there were no differences in median vancomycin trough values or the number of patients who had troughs >15 mg/L or >20 mg/L between the VC and VPT groups, additional analyses were performed to further assess the impact of vancomycin trough on incidence of AKI (Figures 3a, 3b). Interestingly, when the trough was dichotomized, there was no association between vancomycin trough and AKI for patients in the VPT group (trough <15 mg/L or ≥15 mg/L). Additionally, there was no association when troughs were categorized into 3 ascending groups: <15, 15–20, or >20 mg/L.

Conversely, a direct relationship was seen between vancomycin trough and AKI among patients in the VC group. When the vancomycin troughs were dichotomized, AKI occurred in 1/76 (1%) patients with median trough values <15 mg/L vs 20/160 (13%) of patients with values ≥15 mg/L; *P* = 003. Additionally, when vancomycin troughs were analyzed in ascending categories, a significant association was also seen. AKI occurred in 1% of patients with troughs <15 mg/L, in 5% (4/83) of patients with troughs of 15–20 mg/L, and in 21% (16/77) of patients with median troughs >20 mg/L. AKI rates among patients in the VC group were significantly different when patients with troughs of <15 mg/L were compared to patients with troughs >20 mg/L (*P* = .0001) and when patients with vancomycin troughs of 15–20 mg/L were compared to patients with troughs >20 mg/L (*P* = .003).

DISCUSSION

Rates of AKI among patients receiving VPT were approximately 3 times greater than rates in patients receiving VC, regardless of type of AKI definition used. In multivariate modeling and controlling for residual differences between these 2 closely matched groups, receipt of VPT was associated with a greater than 4-fold increased risk of AKI. These findings are particularly robust and convincing as, unlike previous analyses comparing toxicity risk in patients on VPT and VC, this analysis was adequately powered and groups were matched on 5 widely recognized risk factors for AKI in patients receiving vancomycin.

Table 1. Baseline Characteristics of Cohort Comparing Patients Receiving Vancomycin and piperacillin–Tazobactam Combination to Patients Receiving Vancomycin–Cefepime Combination

Variable	Vancomycin–Cefepime n = 279 (%)	Vancomycin and Piperacillin–Tazobactam n = 279 (%)	Odds Ratio (95% Confidence Interval)	*P* Value
Age, y[a]	56.5 ± 16.4	55.3 ± 16.8		.39
Female	153 (55)	128 (46)	0.69(0.50–0.97)	**.034**
Race				**<.0001**
White	56 (20)	93 (33)		**.0005**
Black	191 (68)	175 (63)		
Others	32 (11)	11 (4)	1.98 (1.35–2.92)	
Admission source	226 (81)	242 (87)	1.53 (0.97–2.42)	**.005**
Home	30 (11)	31 (11)		.07
Nursing home	23 (8)	6 (2)		
Other hospital	226 (81)	242 (87)		
Height, cm[a]	170 ± 10	171 ± 11		.34
Median weight, kg	74 (63.8–90)	78.4 (66–95)		.42
Median body mass index, kg/m^2	25 (21.4–30.3)	26.5 (22.5–31.7)		.55
Comorbid conditions				
Myocardial Infarction	24 (9)	13 (5)	0.52 (0.25–1.04)	.06
Congestive heart failure	36 (13)	34 (12)	0.94 (0.56–1.55)	.79
Peripheral vascular disease	26 (9)	30 (11)	1.17 (0.67–2.04)	.57
Dementia	32 (11)	23 (8)	0.69 (0.39–1.22)	.20
Chronic pulmonary disease	79 (28)	82 (29)	1.05 (0.73–1.52)	.78
Connective tissue disease	22 (8)	10 (4)	0.43 (0.20–0.94)	**.03**
Chronic kidney disease	10 (4)	5 (2)	0.49 (0.16–1.45)	.19
Malignant solid tumor	51 (18)	40 (14)	0.75 (0.47–1.17)	.20
Cerebrovascular disease	42 (15)	29 (10)	0.65 (0.39–1.08)	.10
Liver disease	9 (3)	15 (5)	1.70 (0.73–3.96)	.21
Diabetes mellitus	62 (22)	69 (24)	1.15 (0.77–1.70)	.48
Hypertension	177 (63)	149 (53)	0.66 (0.47–0.93)	**.02**
Median Charlson comorbidity index (IQR)	1 (0–3)	1 (0–3)		.21
Hospital and infection-related variables				
Systemic inflammatory response syndrome criteria[b]				
No sepsis	44 (16)	52 (19)		
Sepsis	166 (60)	159 (57)		
Severe sepsis	62 (22)	48 (17)		
Septic shock	7 (3)	20 (7)		
Any sepsis	235 (84)	227 (81)	0.82 (0.53–1.27)	.37
Severe sepsis/septic shock	69 (25)	68 (24)	0.98 (0.66–1.44)	.92
Intensive care unit stay[b]	63 (23)	58 (21)	0.90 (0.60–1.35)	.61
Mechanical ventilation[b]	43 (15)	44 (16)	1.03 (0.65–1.62)	.91
Median white blood cell count[b]	11.3 (7.7–15.5)	10.5 (7.4–14.4)	0.74 (0.53–1.04)	.06
>10	166 (60)	146 (52)		.08
Mean baseline creatinine[a]	0.86 ± 0.20	0.86 ± 0.21		.64
Median length of stay before combination therapy (IQR)	0 (0.0–3.0)	0 (0.0–2.0)		.63
Infection type and diagnosis				
Physician-diagnosis with positive culture	86 (31)	91 (33)	1.08 (0.76–1.55)	.65
Pneumonia	12 (4)	14 (5)	1.17 (0.53–2.59)	.68
Endocarditis	4 (1)	2 (1)	0.49 (0.09–2.73)	.42
Intraabdominal infection	5 (2)	9 (3)	1.82 (0.60–5.51)	.28
Skin/soft tissue infection	21 (8)	37 (13)	1.88 (1.07–3.29)	**.02**
Bone/joint infection	19 (7)	16 (6)	0.83 (0.42–1.65)	.60
Urinary tract infection	11 (4)	8 (3)	0.72 (0.28–1.82)	.48
Bacteremia	22 (8)	25 (9)	1.15 (0.63–2.09)	.65
Catheter-associated bloodstream infection	6 (2)	2 (1)	0.33 (0.06–1.64)	.17
Other/unknown	4 (1)	3 (1)	0.75 (0.16–3.37)	.70
Invasive infection[c]	35 (13)	32 (12)	0.90 (0.54–1.50)	.69

Table 1. Continued

Variable	Vancomycin–Cefepime n = 279 (%)	Vancomycin and Piperacillin–Tazobactam n = 279 (%)	Odds Ratio (95% Confidence Interval)	*P* Value
Polymicrobial infection	36 (13)	40 (14)	1.13 (0.69–1.83)	.62
Pathogens				
Gram-positive bacteria	50 (18)	60 (22)	1.25 (0.83–1.90)	.28
Methicillin-resistant *Staphylococcus aureus*	23 (8)	16 (6)	0.68 (0.35–1.31)	.25
Methicillin-susceptible *Staphylococcus aureus*	7 (3)	14 (5)	2.05 (0.81–5.15)	.13
Gram-negative bacteria	51 (18)	43 (15)	0.81 (0.52–1.27)	.37
Pseudomonas	5 (2)	13 (5)	2.67 (0.94–7.59)	.06
Enterobacteriaceae	48 (17)	31 (11)	0.60 (0.37–0.97)	**.04**
Concomitant nephrotoxins				
Median number of nephrotoxins (IQR)	1 (0–2)	1 (0–2)	0.98 (0.82–1.17)	.86
Vasopressors	9 (3)	16 (6)	1.82 (0.79–4.20)	.16
Aminoglycoside	10 (4)	16 (6)	1.64 (0.73–3.67)	.23
Colistin	7 (3)	2 (1)	0.28 (0.06–1.36)	.12
Angiotensin converting enzyme inhibitors/ angiotensin II receptor blockers	76 (27)	70 (25)	0.89 (0.61–1.30)	.56
Diuretics	78 (28)	75 (27)	0.95 (0.65–1.37)	.78
Intravenous contrast	76 (27)	74 (27)	0.96 (0.66–1.40)	.85
Vancomycin dosing and monitoring				
Loading dose given	237 (85)	233 (84)	0.89 (0.57–1.42)	.64
Loading dose, mg[a]	1544.8 ± 762.3 (n = 237)	1610.2 ± 827.6 (n = 233)		.12
Vancomycin dose [a]	2818 ± 1202	2968 ± 1320		.21
Median trough before AKI[d] (IQR)	17.7 (13.4–20.9)	17.3 (12.6–21.6)		.98
MT before AKI >15[d]	160 (68) n = 236	146 (65) n = 225		.55 .55
MT before AKI >20[d]	77 (33) n = 236	80 (27) n = 225		

Statistically significant values are shown in bold.

Abbreviations: AKI, acute kidney injury; IQR, interquartile range; MT, median trough.

[a]Data are presented as mean ± standard deviation. The vancomycin maintenance dose listed is the first maintenance vancomycin dose, as subsequent doses were based on serum concentrations.

[b] Variables such as systemic inflammatory response syndrome criteria, intensive care unit stay, mechanical ventilation, and wild blood cell count were assessed during a window period of 2 days prior to and 2 days after initiation of combination therapy.

[c] Invasive infections were defined as presence of pneumonia or endocarditis or bone/joint infection.

[d] Data based on median troughs before AKI in patients with AKI and includes median troughs for entire duration of therapy in patients without AKI.

These findings are strengthened by 3 additional important and notable findings. First, among patients who developed AKI, the onset was more rapid in VPT patients compared to VC patients (3 days vs 5 days; $P < .0001$.) Second, the daily rate of AKI among the at-risk population remained higher throughout the first week of therapy among VPT patients. This rapid onset and persistently increased AKI risk are both consistent with VPT being more toxic than VC.

The third finding supporting an association between VPT and increased toxicity was both interesting and unexpected. Data from this study show discordance in the impact of vancomycin troughs on toxicity in patients receiving VPT compared to those receiving VC. Among patients receiving VPT, there was no discernable impact of vancomycin trough on the incidence of AKI. Conversely, a distinct trough–toxicity association was noted in patients receiving VC. These discordant trough associations strengthen the finding that the VPT combination was a significant driver of AKI. These data suggest that the concomitant use of VPT had such a nephrotoxic effect that it muted the impact of vancomycin trough concentrations on AKI. However, when patients received VC (and the toxic effect of VPT was not present), the association between vancomycin troughs and AKI was apparent. These findings could help to explain the discordant literature with respect to the impact of vancomycin trough on AKI, as the type of concomitant antipseudomonal therapy received by patients is rarely reported, let alone controlled for. Of note, the associations between vancomycin trough and AKI are particularly robust, as only trough values obtained before the onset of AKI were included. Because elevated vancomycin troughs that occurred as a result of AKI were excluded, the association between vancomycin trough and AKI was unbiased.

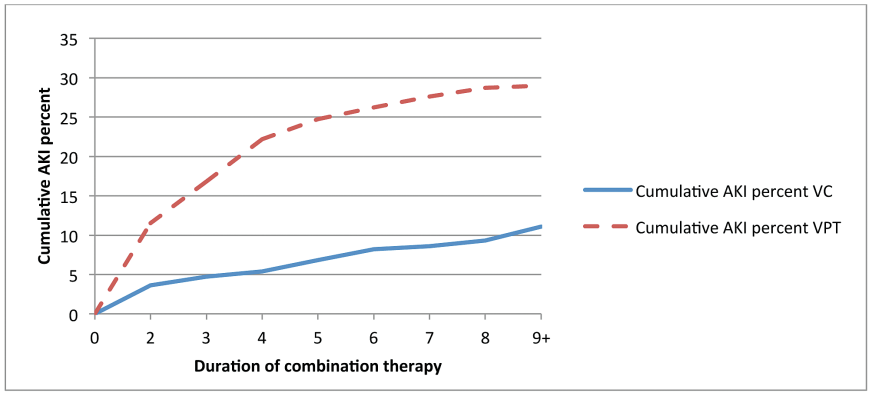


Figure 1. Comparison of cumulative rates of acute kidney injury in patients receiving combination therapy with vancomycin–cefepime and those receiving vancomycin and piperacillin–tazobactam. Abbreviations: AKI, acute kidney injury; VC, vancomycin–cefepime; VPT, vancomycin and piperacillin–tazobactam.

The findings of this study are largely consistent with those found in other studies that analyzed comparative AKI risks of VPT and VC. In a smaller analysis, Gomes and colleagues demonstrated similar findings, with 35% of VPT and 13% of VC patients developing AKI [3]. In a propensity score-matched subgroup, VPT was independently associated with increased AKI risk (OR, 5.67; 95% CI, 1.66–19.33). Similarly, in an analysis that was conducted to assess the impact of generic vancomycin product on development of AKI, Sutton and colleagues reported concomitant VPT to be the strongest predictor of AKI in the cohort (OR, 3.97; 95% CI, 1.66–9.50) [11].

However, the association between VPT and AKI is not a universal finding. Although Moenster and colleagues reported that AKI occurred in 29% of patients on VPT and 13% of patients on VC, this difference failed to reach statistical significance (OR, 3.45; 95% CI, 0.96–12.4) [12]. Importantly, the study was underpowered, and numerically these findings are consistent with those from the aforementioned studies. Hammond and colleagues also recently analyzed comparative toxicity rates in an ICU population. In their analysis AKI was reported in 33% of patients on VPT and 29% of patients on VC; $P = .65$ [4]. It warrants mention that this study was powered to detect a difference in AKI rates of 36.5% vs 15% in the 2 groups and therefore was underpowered to identify more subtle differences in AKI rates, particularly in an ICU population with competing AKI risks.

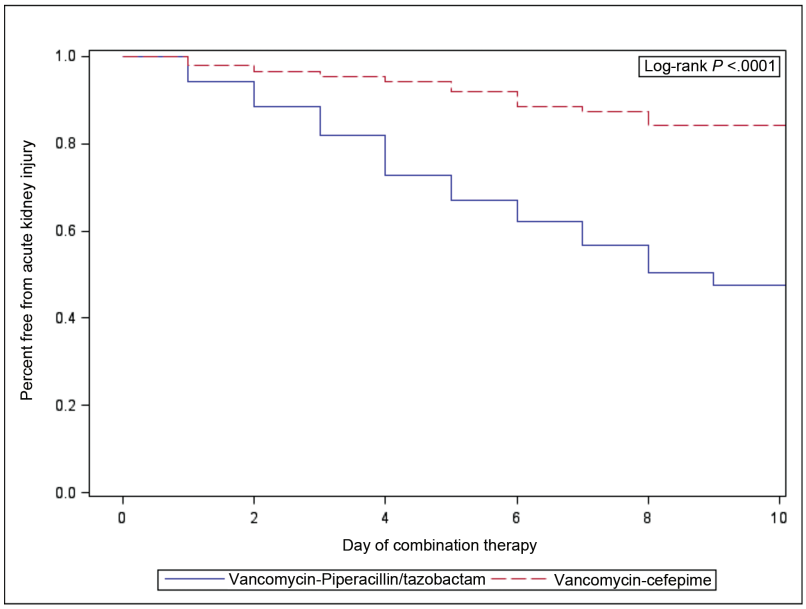


Figure 2. Kaplan–Meier survival analysis for acute kidney injury as a function of treatment group.

Table 2. Outcomes Associated With Receipt of Vancomycin Plus Piperacillin–Tazobactam Combination Therapy Compared to Receipt of Vancomycin Plus Cefepime

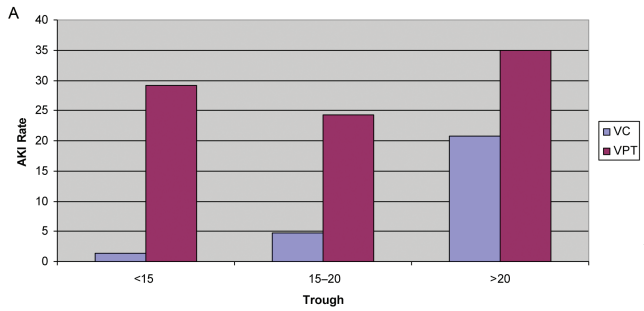
Variable	Vancomycin–Cefepime n = 279 (%)	Vancomycin Plus Piperacillin–Tazobactam n = 279 (%)	Bivariate HR (95% CI)	*P* Value	Multivariate Adjusted HR (95% CI)	*P* Value
RIFLE criteria						
AKI any class	31 (11.1)	81 (29.0)	4.00 (2.59–6.18)	**<.0001**	4.27 (2.73–6.68)[a]	**<.0001**
Risk	12 (4.3)	40 (14.3)				
Injury	8 (2.9)	21 (7.5)				
Failure	11 (3.9)	20 (7.2)				
AKIN criteria						
AKI any stage	39 (13.9)	89 (31.9)	3.49 (2.35–5.18)	**<.0001**		
Stage 1	20 (7.2)	48 (17.2)				
Stage 2	8 (2.9)	21 (7.5)				
Stage 3	11(3.9)	20 (7.2)				
AKI per Vancomycin consensus guidelines	23 (8.2)	67 (24.0)	4.44 (2.69–7.32)	**<.0001**		
AKI requiring hemodialysis	3 (1.1)	2 (0.7)	0.66 (0.11–4.00)	**.65**		
Median length of stay after initiation of combination therapy (interquartile range)	6 [4–11]	8 [5–12]		**.01**		
Mortality	24 (8.6)	16 (5.7)	0.64 (0.34–1.24)	**.19**		

Statistically significant values are shown in bold.

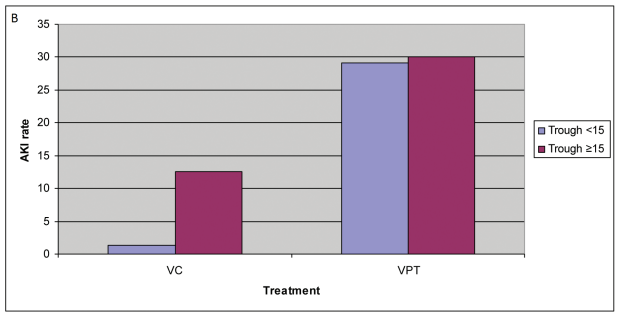
Abbreviations: AKI, acute kidney injury; AKIN, acute kindey injury network; CI, confidence interval; HR, hazard ratio; RIFLE, risk, injury, failure, loss, end stage.

[a] Controlling for race, gender, admission from home, comorbid conditions, baseline serum white blood cell count >10, 000/μL, and source of infection being skin or soft tissue.

The data presented here are robust, overcome several limitations found in the previous literature, and convincingly demonstrate that, compared to VC, combination therapy with VPT is associated with a higher overall incidence of AKI, a more rapid onset of AKI, and a persistently increased daily AKI risk throughout the first week of therapy. Despite the robustness of our methodology, there are a few limitations. This was a single-center, retrospective analysis and is thus subject to the inherit biases associated with this type of study design, and the results should be confirmed in other patient populations. In addition, only approximately 20% of patients in this study were cared for in the ICU; therefore,



Median trough value	Toxicity rates	*P* value vs 15–20 mg/L	*P* value vs >20 mg/L
Vancomycin/cefepime			
<15 mg/L	1/76 (1)	0.37	0.0001
15 – 20 mg/L	4/83 (5)	NA	0.0003
>20 mg/L	16/77 (21)	0.0003	NA
Vancomycin/piperacillin-tazobactam			
<15 mg/L	23/79 (29)	0.57	0.5
15 – 20 mg/L	16/66 (24)	NA	0.2
>20 mg/L	28/80 (35)	0.2	NA



	<15 mg/L	≥15 mg/L	*P*
Vancomycin/cefepime	1/76 (1)	20/160 (13)	0.003
Vancomycin/ piperacillin-tazobactam	23/79 (29)	44/146 (30)	1.0

Figure 3. A, Acute kidney injury (AKI) rates as a function of vancomycin troughs. B, AKI rates in patients with median troughs <15 mg/L vs ≥ 15 mg/L.Abbreviations: AKI, acute kidney injury; NA, not applicable; VC, vancomycin–cefepime; VPT, vancomycin and piperacillin–tazobactam.

the results might not be generalizable to the ICU patient population. Furthermore, while the definition of combination therapy used in this manuscript is rational (≥48 hours of combination therapy where each agent was started within 24 hours of the other), definitions used by investigators in other analyses differ slightly (ranging from a requirement of administration of the combination for ≥48–72 hours, with or without the requirement that the agents were started within 48 hours of one other). However, these relatively minor differences are unlikely to explain differences between the findings presented here and those in prior publications. Finally, we chose to exclude patients with baseline renal insufficiency. Patients with baseline renal insufficiency represent an important patient population at risk for developing AKI and warrant evaluation in future studies.

In conclusion, combination therapy with VPT was independently associated with a 4-fold increased risk of AKI compared to combination therapy with VC. Additionally, AKI with VPT occurred in a more rapid fashion. Despite this rapid onset of AKI, there are opportunities for providers to limit the incidence of this adverse event. Data recently published by our group [10] demonstrated that the highest daily incidence of AKI among patients receiving VPT occurred on day 4 and day 5 of therapy. Therefore, timely de-escalation or discontinuation of 1 or both of the combination agents would likely mitigate AKI risk. However, given the association between VPT and increased AKI risk, it is critical that clinicians consider all risks and benefits of therapy (both efficacy and toxicity) when selecting empiric combination regimens. Clinicians might choose an alternative to piperacillin–tazobactam in settings where vancomycin is coadministered. If antibiogram data demonstrate an advantage with regard to activity against likely gram-negative pathogens of empiric piperacillin–tazobactam, clinicians might combine piperacillin–tazobactam with an alternative gram-positive agent. Because overuse of vancomycin alternatives might be concerning from a stewardship perspective, one approach might be to limit use of combination therapy with vancomycin alternatives and piperacillin–tazobactam to patients who are hemodynamically unstable and thus more likely to be significantly harmed by ineffective empiric gram-negative coverage, while using vancomycin plus cefepime in more stable patients.

Note

Potential conflicts of interest. Authors certify no potential conflicts of interest. The authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Magill SS, Edwards JR, Beldavs ZG, et al; Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Prevalence of antimicrobial use in US acute care hospitals, May–September 2011. JAMA **2014**; 312:1438–46.
2. Burgess LD, Drew RH. Comparison of the incidence of vancomycin-induced nephrotoxicity in hospitalized patients with and without concomitant piperacillin-tazobactam. Pharmacotherapy **2014**; 34:670–6.
3. Gomes DM, Smotherman C, Birch A, et al. Comparison of acute kidney injury during treatment with vancomycin in combination with piperacillin-tazobactam or cefepime. Pharmacotherapy **2014**; 34:662–9.
4. Hammond DA, Smith MN, Painter JT, Meena NK, Lusardi K. Comparative incidence of acute kidney injury in critically ill patients receiving vancomycin with concomitant piperacillin-tazobactam or cefepime: a retrospective cohort study. Pharmacotherapy **2016**; 36:463–71.
5. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee Including the Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med **2013**; 39:165–228.
6. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
7. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical Care (London, England). **2004**;8:R204–12.
8. Mehta RL, Kellum JA, Shah SV, et al; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care **2007**; 11:R31.
9. Rybak MJ, Lomaestro BM, Rotschafer JC, et al. Vancomycin therapeutic guidelines: a summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis **2009**; 49:325–7.
10. Karino S, Kaye KS, Navalkele B, et al. Epidemiology of acute kidney injury among patients receiving concomitant vancomycin and piperacillin-tazobactam: opportunities for antimicrobial stewardship. Antimicrob Agents Chemother **2016**; 60:3743–50.
11. Sutton JD, Mynatt RP, Kaye KS, Murray KP, Rybak MJ, Pogue JM. Nephrotoxicity comparison of two commercially available generic vancomycin products. Antimicrob Agents Chemother **2015**; 59:5470–4.
12. Moenster RP, Linneman TW, Finnegan PM, Hand S, Thomas Z, McDonald JR. Acute renal failure associated with vancomycin and β-lactams for the treatment of osteomyelitis in diabetics: piperacillin-tazobactam as compared with cefepime. Clin Microbiol Infect **2014**; 20:O384–9.