



# A retrospective cohort study assessing acute kidney injury and renal recovery among septic patients empirically treated with vancomycin piperacillin–tazobactam versus vancomycin cefepime

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## Abstract

Vancomycin plus piperacillin–tazobactam (VPT) is a commonly used antimicrobial regimen for septic patients. VPT is more nephrotoxic than other regimens such as vancomycin plus cefepime (VC) when given over several days. This risk of nephrotoxicity is less clear when VPT is given for initial empiric therapy in sepsis and de-escalated quickly based on evolving clinical information. The objective of this study was to assess nephrotoxicity among septic patients empirically treated with either VPT or VC at initial clinical presentation. We conducted a retrospective study of septic patients who received VPT or VC within 12 h of presentation to the emergency department. The primary outcomes were acute kidney injury (AKI) and renal recovery 72 h after presentation. For the total of 418 patients, 306 received VPT and 112 received VC. Rates of AKI at 72 h were 15.2% for VPT patients and 11.0% for VC patients [ $p=0.44$ ]. Among patients with AKI at presentation, 16.3% of VPT patients had AKI at 72 h compared to 8.9% of VC patients [ $p=0.19$ ]. Among those without AKI at presentation, 14.2% VPT patients and 16.7% VC patients had AKI at 72 h [ $p=0.71$ ]. Renal recovery rates for patients with AKI at presentation were 42.3% for VPT patients versus 40.3% for VC patients [ $p=0.78$ ]. In-hospital renal replacement therapy occurred in 6.2% VPT patients and 0.9% VC patients [ $p=0.024$ ]. Therefore, initial empiric therapy with VPT in sepsis may not confer increased risk of AKI when de-escalated appropriately.

**Keywords** Sepsis · Acute kidney injury · Anti-bacterial agents · Critical care · Septic shock · Renal insufficiency

## Abbreviations

AKI Acute kidney injury  
VPT Vancomycin and piperacillin–tazobactam  
VC Vancomycin and cefepime  
RRT Renal replacement therapy

SOFA Sequential organ failure assessment  
MAP Mean arterial pressure

## Introduction

Sepsis accounts for approximately 6% of hospitalizations in the United States, with mortality rates of approximately 15–31% [1, 2]. Due to their severity of illness, septic patients require urgent and often broad-spectrum antibiotics to decrease mortality [3, 4]. Prompt and appropriate antimicrobial therapy can also reduce the risk of sepsis-associated acute kidney injury (AKI), a frequent comorbidity of septic patients that occurs in 22–51% of patients with severe sepsis [5, 6]. However, nephrotoxic medications can also contribute to AKI in sepsis, accounting for approximately 20% of cases [6]. Therefore, an antimicrobial regimen that provides adequate broad-spectrum coverage but mitigates the risk of AKI could help reduce the deleterious effects of

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AKI in septic patients, such as increased illness severity and mortality [6].

The combination of vancomycin plus piperacillin–tazobactam (VPT) is one of the more frequently used broad-spectrum empiric regimens for sepsis. Separately, they are two of the four most used antimicrobials in U.S. hospitals [7]. However, using VPT for more than 48 or 72 h increases the risk of nephrotoxicity [8–13], with possibly the greatest risk at day 5 of therapy [14]. The evidence for nephrotoxicity with brief use of VPT is less robust, with one study evaluating use of VPT versus vancomycin plus cefepime (VC) for less than 72 h suggesting no substantial increase in nephrotoxicity with VPT use [15].

VPT nephrotoxicity may prompt physicians to treat sepsis empirically with VC, but this substitution is far from a simple solution as cefepime is associated with other clinical effects. While patients with reduced renal function may seem ideal to receive VC, they are at increased risk of cefepime-associated neurotoxicity [16]. Cefepime also lacks the anaerobic organism coverage that piperacillin–tazobactam provides, which may be desired in certain clinical scenarios. A large reduction in AKI may counterbalance these disadvantages, but the extent of nephrotoxicity reduction with VC is not well described for initial empiric therapy in septic patients.

When nephrotoxicity from VPT is apparent in septic patients, de-escalating empiric antibiotic therapy within a 72-h period may be a feasible strategy. Empiric regimens can often be tailored based on evolving clinical information such as polymerase chain reaction testing of the nares for Methicillin resistant *Staphylococcus aureus* (MRSA), culture data, and other clinical testing. Whether such test findings reduce the duration of VPT use and mitigate nephrotoxicity is unclear. Further, in circumstances where septic patients can be de-escalated based on clinical data, it is uncertain whether initial empiric therapy with VPT results in a higher rate of nephrotoxicity compared to VC.

Furthermore, VPT and VC have not been adequately compared on renal recovery in patients presenting to the emergency department with sepsis-mediated AKI. While there are varying definitions of renal recovery, early recovery of renal function after AKI is associated with both improved survival and reduced long-term major adverse kidney events [17–19]. Specific to bacterial sepsis-mediated AKI, prompt and appropriate antibiotics are associated with renal recovery [18]. Thus, an antimicrobial regimen that provides appropriate coverage promptly without impeding renal recovery could confer downstream benefits.

The purpose of this study was to assess rates of AKI and early renal recovery for patients presenting to the emergency department with sepsis who are treated empirically with VPT versus VC therapy. We also evaluated other critical care outcomes associated with these two treatment strategies

– e.g., ventilator-free days, length of hospital and ICU stay, and mortality. We hypothesized that VPT would result in more nephrotoxicity than VC, but that the two groups would not differ on other critical care outcomes.

## Methods

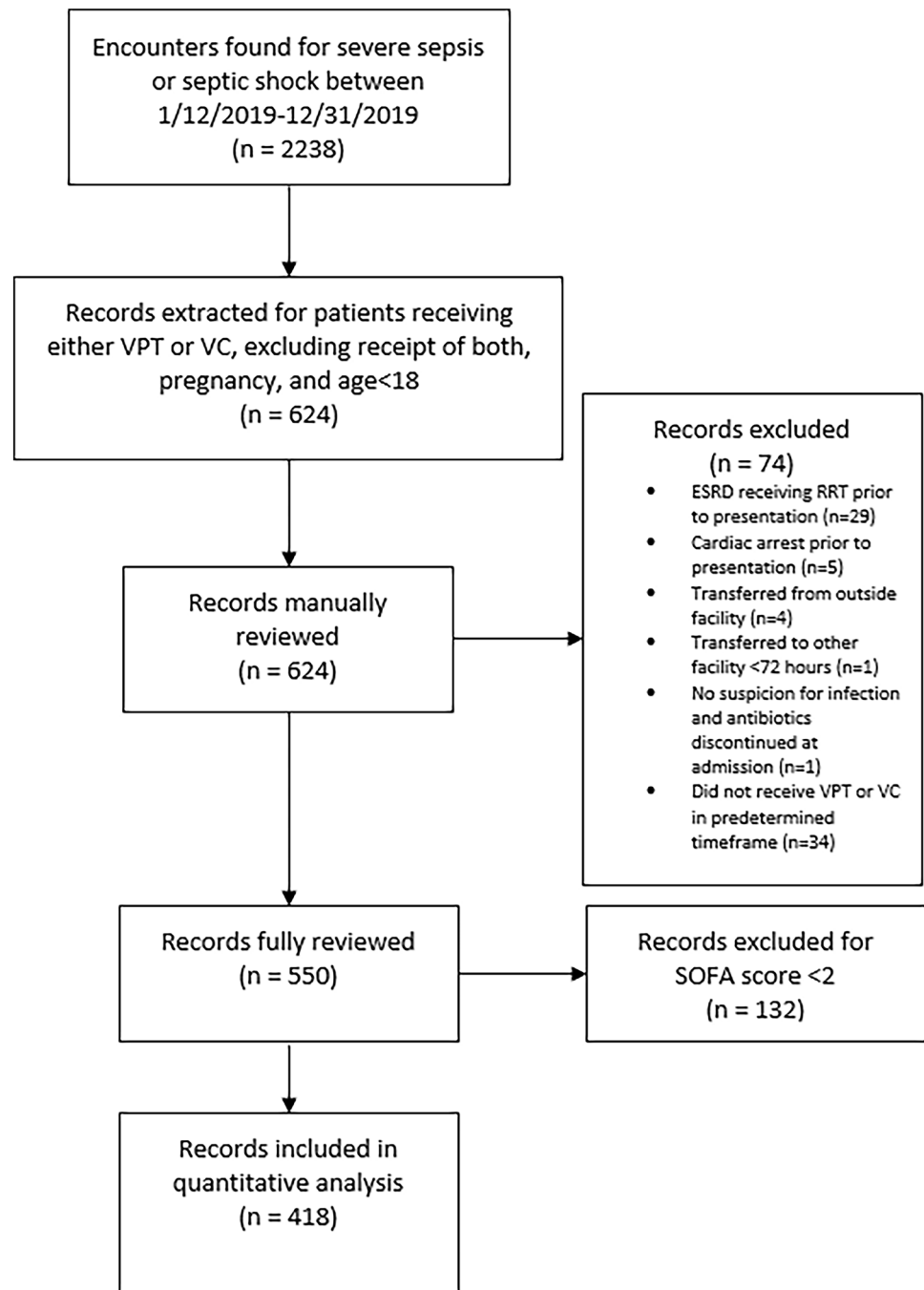
### Study population and data sources

We conducted a retrospective study of septic patients. The study was approved by our Institutional Review Board. Every patient receiving an admitting ICD-10 diagnosis of severe sepsis or septic shock after presenting to our tertiary care facility emergency department between January 12, 2019 through December 31, 2019 was assessed for study inclusion. The hospital is in an urban setting, contains 848 beds, and includes approximately 100 intensive care unit beds.

We identified 2238 consecutive patients admitted with an ICD-10 diagnosis of severe sepsis or septic shock, two diagnoses that correspond with the most recent guidelines for the definition of sepsis [20]. Figure 1 shows the inclusion and exclusion criteria for the study. We included patients who (1) presented to the emergency department with a diagnosis of sepsis, (2) were initiated on or continued antibiotics at admission, and (3) received either VPT or VC within the first 12 h of presentation. Patients were excluded if (1) less than 18 years of age, (2) pregnant, (3) in end-stage renal disease (ESRD) and receiving renal replacement therapy (RRT) prior to admission, (4) transferred from another facility, (5) transferred to another facility within 72 h of presentation, or (6) presented after cardiac arrest. Patients were grouped in the VPT or VC arm by the receipt of each regimen in the first 12 h of presentation to the emergency department. Patients who received both regimens in the first 24 h of presentation were excluded. Most variables were extracted from the electronic medical record and validated by manual review of sample charts. When manual review found errors for antibiotics, corrections were made. These instances were often due to order discontinuation, delays in administration, or orally formulated vancomycin.

### Definition of variables

Based on current guidelines [20], sepsis was defined as a modified sequential organ failure assessment (SOFA) score of 2 or greater. Septic shock was defined as vasopressor requirement to maintain mean arterial pressure (MAP) > 65 mmHg and repeat lactate > 2 mmol/L after initial resuscitation. A modified SOFA score was reported using the SpO<sub>2</sub>/FiO<sub>2</sub> ratio as a substitute for the PaO<sub>2</sub>/FiO<sub>2</sub> ratio, a validated alternative [21]. The

**Fig. 1** Patient inclusion and exclusion

most abnormal value during each assessment period was recorded. The initial modified SOFA score was assessed in the first six hours since presentation to the emergency department, while the modified SOFA score at 72 h was assessed at hours 66 to 78 since presentation to the emergency department. Acute kidney injury diagnosis and staging were assessed according to Kidney Disease Improving Global Outcomes (KDIGO) criteria [22]. Urine output was omitted from the criteria due to heterogeneous documentation. Chronic Kidney Disease (CKD) was also

defined according to KDIGO criteria, using an estimated glomerular filtration rate (eGFR) of  $< 60 \text{ mL/min/1.73 m}^2$  calculated via the Modification of Diet in Renal Disease (MDRD) method [23]. We defined renal recovery as a 33% reduction in serum creatinine, a criterion proposed for the retrospective diagnosis of early renal recovery [24]. We assessed renal recovery at the 72-h period as early renal recovery in this time frame is associated with reduced long-term major adverse kidney events [19]. While the 33% reduction criterion was not specifically validated for

this timeframe, we favored this definition, which may better represent meaningful GFR changes at high creatinine values.

Secondary outcomes were evaluated either during the 72-h assessment period or during the entire hospitalization, with the assessment period specified with each variable. Intubation during hospitalization was defined as a new endotracheal intubation placed by emergency medical services or since presentation to the emergency department. Ventilator-free days were assessed for patients with intubation during hospitalization and was assessed as 28 minus days spent on mechanical ventilation since intubation. Patients who died within 28 days of intubation were quantified as 0 ventilator-free days. Vancomycin use at 72 h was defined as the absence of vancomycin discontinuation prior to the 72-h assessment period, regardless of dosing. Same VPT or VC regimen at 72 h was defined as the absence of discontinuation of both vancomycin plus piperacillin–tazobactam and vancomycin plus cefepime prior to the 72-h assessment period, regardless of dosing.

### Antibiotic dosing and oversight

Piperacillin-tazobactam dosing was according to our facility guidelines. Our standard dosing guidelines for piperacillin–tazobactam administration are an extended infusion of either 3.375 g or 4.5 g every 8 hours. Vancomycin and cefepime are dosed at the discretion of the primary provider or by referral to pharmacy for dosing recommendations. The vancomycin dosing protocol utilized trough measurements for monitoring. Antimicrobials administered in the ICU were reviewed every weekday by a clinical pharmacist rounding with the critical care team. The antimicrobial stewardship team, including an infectious disease physician and infectious disease pharmacist, prospectively audited patients receiving multiple antibiotics every weekday. Antibiotics were de-escalated or adjusted at the discretion of the primary provider or at the recommendation of the antimicrobial stewardship program. Nasal MRSA polymerase chain reaction (PCR) was routinely used as a method to de-escalate MRSA coverage in respiratory infections, as this has been shown to safely reduce the duration of vancomycin use [25, 26].

### Statistical analysis

An a priori calculation was performed to determine the goal sample size for the study. Based on AKI incidences reported in earlier observational studies [8–14], at 80% power ( $\beta = 0.20$ ) and  $\alpha = 0.05$ , a sample size of 330 with a 1:2 enrollment ratio for VC to VPT was needed to claim a 50% relative risk reduction of AKI to be statistically significant.

Continuous variables are summarized with the median and interquartile range. Categorical variables are summarized with counts and percentages. For group comparisons involving continuous variables, the Mann–Whitney Test was used since data seldomly followed a normal distribution. The chi-squared test was used for comparisons involving categorical variables. Analyses were conducted using IBM SPSS Statistics 25.0 (IBM, Armonk, NY).

## Results

### Demographic and clinical characteristics

After exclusions, 306 patients were identified in the VPT group, while 112 patients were identified in the VC group. Table 1 compares the demographic and clinical characteristics of the VPT and VC groups. The two groups did not significantly differ on all but two characteristics, repeat lactate and rate of pneumonia as the suspected source of infection. Both variables were higher for the VPT group.

### Primary outcomes

Among 157 VPT patients with AKI at presentation, 129 were available for AKI assessment at 72 h while 56 of 67 VC patients were available (39 patients were discharged or died before 72 h). Among the 129 VPT patients, 16.3% had AKI at 72 h compared to 8.9% of the VC patients [ $p = 0.19$ ]. Among those without AKI at presentation, 14.2% VPT patients and 16.7% VC patients had AKI at 72 h [ $p = 0.71$ ]. The renal recovery rate for patients with AKI at presentation was 42.3% for VPT patients versus 40.3% for VC patients [ $p = 0.78$ ]. Renal replacement therapy during hospitalization occurred in 6.2% VPT patients and 0.9% VC patients [ $p = 0.024$ ]. [Table 2 and Fig. 2].

### Secondary outcomes

Table 2 shows the results for the secondary outcomes, with continuous outcomes reported as median and interquartile range. The VPT group compared to the VC group had higher rates of intubation during hospitalization (26% vs. 14%,  $p = 0.015$ ) while the VC group had higher rates of remaining on the same regimen at 72 h (21% vs. 12%,  $p = 0.013$ ) and receiving vancomycin at 72 h (28% vs. 18%,  $p = 0.030$ ). Otherwise, the two groups did not differ on the secondary outcomes: change in SOFA score (VPT =  $-1 \pm 3$  vs. VC =  $-1 \pm 3$ ,  $p = 0.97$ ), hospital length of stay (VPT =  $7.6 \pm 7.6$  vs. VC =  $7.5 \pm 8.8$  days,  $p = 0.81$ ), ICU LOS (VPT =  $3.8 \pm 4.5$  vs. VC =  $3.1 \pm 4.0$  days,  $p = 0.20$ ), ventilator-free days (VPT =  $19.3 \pm 26.0$  vs. VC =  $18.2 \pm 22.1$  days,  $p = 0.45$ ), vasopressor use at

**Table 1** Demographic and clinical characteristics of 418 septic patients empirically treated with vancomycin piperacillin–tazobactam versus vancomycin cefepime

Demographic and Clinical Characteristics*	VPT N=306	VC N=112	<i>p</i>
<b>Demographic Characteristics</b>			
Age—years	67.0±20	68.5±23	0.85
Sex—female	133 (44)	57 (51)	0.18
Ethnicity			0.15
Caucasian	233 (76)	76 (68)	
Black/African American	68 (22)	35 (31)	
Asian	2 (1)	1 (1)	
Two or more ethnicities	3 (1)	0 (0)	
<b>Clinical Characteristics</b>			
Body Mass Index <sup>a</sup>	27.2±9.2	27.5±10.4	0.52
Time to admission—hours	4.6±1.7	4.5±1.7	0.78
Time to first antibiotic—hours	1.9±1.8	2.2±2.2	0.07
History of hepatic disease	39 (13)	9 (8)	0.18
History of congestive heart failure	58 (19)	21 (19)	0.96
<b>Suspected source of infection</b>			
Pneumonia	150 (49)	41 (37)	0.024
Urinary tract infection	29 (10)	16 (14)	0.16
Skin and soft tissue	28 (9)	11 (10)	0.84
Intra-abdominal	14 (5)	6 (5)	0.74
Endocarditis/bacteremia	12 (4)	2 (2)	0.44
Other	3 (1)	1 (1)	1.00
Unknown	70 (23)	35 (31)	0.08
Initial SOFA <sup>†</sup> score	5.0±4.0	4.0±4.0	0.25
Initial mechanical ventilation	45 (15)	10 (9)	0.12
Fluid volume in first 6 h—mL	2000±1800	2000±1531	0.82
Vasopressor within first 6 h	29 (10)	11 (10)	0.92
Initial lactate <sup>b</sup> – mmol/L	2.70±2.90	2.65±2.25	0.43
Repeat lactate <sup>c</sup> – mmol/L	2.30±2.30	1.85±1.53	0.034
Septic shock	14 (5)	8 (7)	0.30
Creatinine prior to admission <sup>d</sup> —mg/dL	0.8±0.5	0.8±0.5	0.31
Initial creatinine—mg/dL	1.2±1.0	1.3±1.1	0.25
Estimated GFR <sup>‡</sup> prior to admission <sup>e</sup> —mL/min/1.73 m <sup>2</sup>	86±71	87±77	0.52
Initial estimated GFR <sup>‡</sup> —mL/min/1.73 m <sup>2</sup>	58±51	55±56	0.18
Acute kidney injury at presentation	157 (51)	67 (60)	0.12
Acute kidney injury stage at presentation			0.07
No acute kidney injury	149 (49)	45 (40)	
Stage 1	83 (27)	26 (23)	
Stage 2	40 (13)	25 (22)	
Stage 3	34 (11)	16 (14)	

\*Continuous variables are reported as median ± interquartile range; categorical variables are reported as count (percentage)

\*\*Mann–Whitney Test for continuous variables; chi-squared test for categorical variables

Sample sizes: <sup>a</sup>VPT=253; VC=97

<sup>b</sup>VPT=298; VC=110

<sup>c</sup>VPT=267; VC=98

<sup>d</sup>VPT=234; VC=86

<sup>e</sup>VPT=234; VC=86

<sup>†</sup>Sequential Organ Failure Assessment

<sup>‡</sup>Glomerular filtration rate

**Table 2** Outcomes of 418 septic patients empirically treated with vancomycin piperacillin–tazobactam versus vancomycin cefepime

Outcomes*	VPT N=306	VC N=112	<i>p</i>
<b>Primary Outcomes</b>			
AKI at presentation with AKI at 72 hours <sup>a</sup>	21 (16.3)	5 (8.9)	0.19
No AKI at presentation with AKI at 72 hours <sup>b</sup>	18 (14.2)	6 (16.7)	0.71
AKI at presentation with renal recovery at 72 hours <sup>c</sup>	66 (42.3)	27 (40.3)	0.78
Renal replacement therapy during hospitalization	19 (6.2)	1 (0.9)	0.024
<b>Secondary Outcomes</b>			
<b>Secondary Renal Outcomes</b>			
Change in estimated GFR‡ from initial to 72 hours <sup>e</sup>	15 ± 40	15 ± 43	0.49
Creatinine at 72 hours <sup>e</sup>	0.9 ± 0.7	1.1 ± 1.1	0.55
Acute kidney injury stage at 72 hours <sup>f</sup>			0.14
No AKI	217 (85)	81 (88)	
Stage 1	24 (9)	9 (10)	
Stage 2	4 (2)	2 (2)	
Stage 3	11 (4)	0 (0)	
Time to renal replacement therapy – hours <sup>7</sup>	38 ± 75	74 ± 0	0.70
RRT at 72 h	10 (3)	0 (0)	0.12
RRT discontinued <sup>g</sup>	6 (32)	0 (0)	1.00
<b>Mechanical Ventilation</b>			
Intubated during hospitalization	78 (26)	16 (14)	0.015
Ventilator-free days	19.3 ± 26.0	18.2 ± 22.1	0.45
<b>Antibiotic Use at 72 Hours</b>			
Same VPT or VC regimen at 72 h	36 (12)	24 (21)	0.013
Vancomycin use at 72 h	55 (18)	31 (28)	0.030
<b>Other Secondary Outcomes</b>			
Change in SOFA† score <sup>d</sup>	-1 ± 3	-1 ± 3	0.97
Vasopressor use at 72 h	11 (4)	3 (3)	0.88
Hospital length of stay—days	7.6 ± 7.6	7.5 ± 8.8	0.81
ICU length of stay—days	3.8 ± 4.5	3.1 ± 4.0	0.20
In-hospital mortality	45 (15)	11 (10)	0.19

\*Continuous variables reported as median ± interquartile range; categorical variables reported as count (percentage)

\*\*Mann–Whitney Test for continuous variables; chi-squared test for categorical variables

\*\*\*Two proportion z-test

Sample sizes: <sup>a</sup>VPT = 129; VC = 56

<sup>b</sup>VPT = 127; VC = 36

<sup>c</sup>VPT = 156; VC = 67

<sup>d</sup>VPT = 265; VC = 92

<sup>e</sup>VPT = 255; VC = 92

<sup>f</sup>VPT = 256; VC = 92

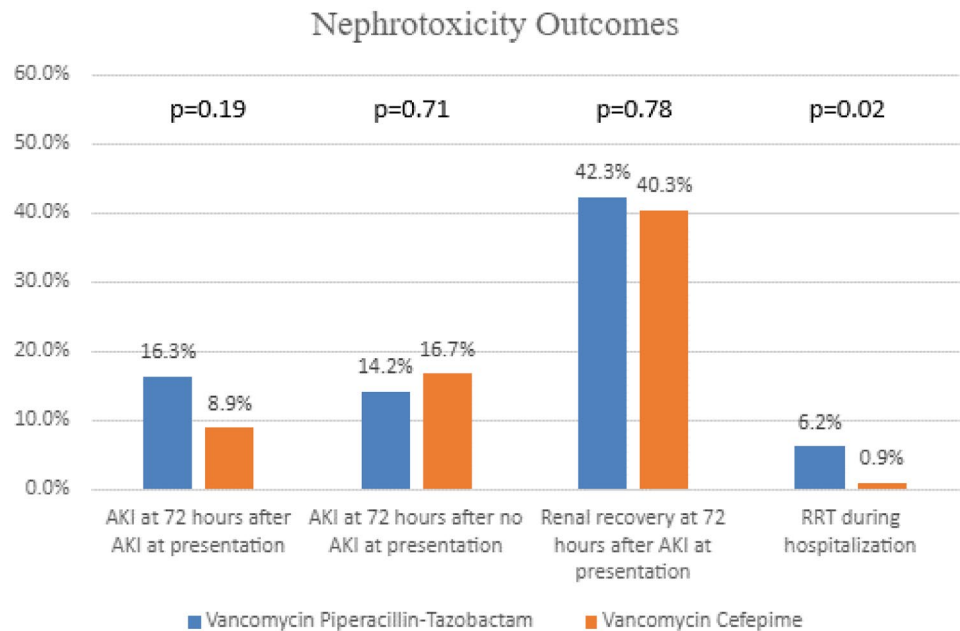
<sup>g</sup>VPT = 19; VC = 1

†Sequential Organ Failure Assessment

72 h (VPT = 4% vs. VC = 3%, *p* = 0.88), change in estimated GFR from initial to 72 h (VPT = 15 ± 40 vs. VC = 15 ± 43 mL/min/1.73 m<sup>2</sup>, *p* = 0.49), creatinine at 72 h (VPT = 0.9 ± 0.7 vs. VC = 1.1 ± 1.1 mg/dL, *p* = 0.55), acute kidney injury stage at 72 h (*p* = 0.14), time to renal replacement therapy (VPT = 38 ± 75 vs. VC = 74 ± 0 h, *p* = 0.70), RRT at 72 h (VPT = 3% vs. VC = 0%, *p* = 0.12),

RRT discontinued (VPT = 32% vs. VC = 0%, *p* = 1.00), and in-hospital mortality (VPT = 15% vs. VC = 10%, *p* = 0.19).

**Fig. 2** Nephrotoxicity outcomes for patients initially treated with either VPT or VC in sepsis.



## Discussion

Our study adds to the evidence on AKI risk for VPT and VC by evaluating patients receiving initial empiric therapy after presenting to the emergency department with sepsis defined by current guidelines. Further, we evaluated renal recovery among septic patients initially presenting with AKI.

We found no increase in AKI or decrease in renal recovery at 72 h with VPT therapy as compared with VC therapy. Prolonged VPT therapy has a 2- to threefold increased risk of AKI compared to VC [8–13]. In our patients, early de-escalation (< 20% receiving the same initial empiric regimen at 72 h) likely accounted for the absence of increased AKI risk. This finding emphasizes the importance of de-escalating broad-spectrum antimicrobial therapy early, when feasible. The lack of differences in demographic and clinical characteristics before and at admission in the VPT or VC groups suggests that clinicians may have chosen a provider-preferred regimen. One notable exception to the lack of differences is the higher rate of pneumonia as the suspected source of sepsis among patients treated with VPT. This difference may indicate some preference for VPT over VC for the treatment of pneumonia.

The risk of VPT nephrotoxicity was less clear for patients with AKI at presentation. Patients who received VPT versus VC had an 83% relative risk increase for AKI at 72 h (VPT: 16.3%; VC: 8.9%) that was not statistically significant but may be clinically meaningful. For patients without AKI at presentation, those who received VPT versus VC had a 15% relative risk reduction for AKI at 72 h (VPT: 14.2%; VC: 16.7%), also not statistically significant.

We found an increased risk of renal replacement therapy during hospitalization for patients who received VPT (19 patients [6.2%]) as compared with VC (1 patient [0.9%]), despite the VC patients demonstrating comparable AKI rates to that of VPT patients. Most patients who received RRT presented with AKI, 84% of VPT patients who received RRT and 100% of VC patients who received RRT. The findings for VPT patients—a 83% relative risk increase for AKI at 72 h for patients with initial AKI and more renal replacement therapy during hospitalization—may indicate that VPT nephrotoxicity is more likely among patients with preceding nephrotoxic insult, even when antimicrobial therapy is de-escalated.

Our study had several limitations that may affect its application to clinical practice. The study was conducted at a single hospital. Consequently, generalizability to other clinical settings should be done with caution. Antimicrobial stewardship at our hospital might also impact generalizability, as not all centers may review antimicrobial use for appropriateness on such a frequent basis. Since this study was a retrospective chart review investigation, data omissions occurred more frequently than in a prospective study. The clinical assessment of renal function also carries limitations. Creatinine and calculated eGFR were used as markers to determine renal function and nephrotoxicity. These surrogates are imperfect, especially in the setting of acute kidney injury of the critically ill. However, they are often used in clinical practice. Urine output was not able to be assessed due to its variable documentation. Lack of a uniform definition of renal recovery in the literature limits the assessment of this clinical outcome. Finally, the study's retrospective design precluded

statements of causation, restricting our findings to correlational relationships.

## Conclusion

Initial empiric therapy with VPT or VC for septic patients presenting to the emergency department did not differ on rates of acute kidney injury and renal recovery at 72 h. Consequently, initial empiric therapy with VPT may not result in more nephrotoxicity than VC for septic patients, provided antimicrobial therapy is de-escalated appropriately.

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## Declarations

**Conflict of interest** None of the authors have conflicts of interest to report with regard to this research project. We have no financial conflicts of interest to disclose as well as no financial support to disclose.

**Disclaimer** The views expressed are those of the authors and do not necessarily reflect the official views of the Wright Patterson Medical Center, United States Air Force, or the Department of Defense. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government.

**Ethics Approval** Ethical approval and informed consent were waived by the local Ethics Committee (IRB) of Wright State University in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

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