Acute Kidney Injury with Piperacillin-tazobactam versus Cefepime in Combination with Vancomycin

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ABSTRACT

Background
Drug-induced nephrotoxicity in the form of acute kidney injury (AKI) is a potential adverse effect of vancomycin, which is commonly prescribed empirically with an antipseudomonal agent. It is unclear if combinations with certain antipseudomonal agents (e.g., piperacillin-tazobactam) are associated with more AKI relative to others.

Methods
This retrospective cohort study conducted at two Veterans Affairs (VA) Medical Centers with differing preferred empiric vancomycin-antipseudomonal regimens aimed to assess the incidence of AKI in patients receiving vancomycin and piperacillin-tazobactam (VPT) at VA Greater Los Angeles Healthcare System (HCS) versus vancomycin and cefepime (VC) at VA Long Beach HCS. Patients who received VPT or VC for at least 48 hours in 2016-2018 were included. AKI definitions were derived from 2012 Kidney Disease Improving Global Outcomes guidelines. Secondary assessments included hospital length of stay, 90-day mortality, and incidence of *Clostridioides difficile* infection (CDI) within 90 days. Patients who developed AKI were further assessed for time-to-onset of AKI, development of chronic kidney disease (CKD) within 90 days, and hemodialysis (HD) dependence within 1 year. Statistical analysis was performed using Fisher's exact and Mann-Whitney U tests where appropriate. Propensity score matching using logistic regression with nearest-neighbor matching was performed to control for potential confounding baseline characteristics.

Results
21/120 patients receiving VPT developed AKI vs. 4/120 receiving VC (17.5% vs. 3.3%, p=0.0005). After propensity score matching, AKI incidence remained significantly higher for VPT patients (15.2% vs. 4.0%, p=0.01). Median length of stay was significantly longer for VPT patients (10 days vs. 8 days, p=0.03). There was no significant difference in time-to-onset of AKI, 90-day mortality, or CDI. No significant difference was found in the development of CKD within 90 days nor the requirement of HD within 1 year.

Conclusion
VPT combination therapy was associated with increased incidence of AKI compared to VC, though 90-day mortality and other outcomes were similar. Advising prescribers about potentially increased risk of AKI with VPT is a viable stewardship intervention.

RESULTS

Table 1. Baseline Characteristics

	Vancomycin and Piperacillin-tazobactam N=120 (%)	Vancomycin and Cefepime N=120 (%)	*P* Value
Age, years, mean ± SD	65 ± 13	67 ± 12	0.14
Male	117 (97.5)	120 (100)	0.25
Race			
White	54 (45)	78 (65)	0.0028
African American	42 (35)	20 (16.7)	0.0018
Hispanic	14 (11.7)	0 (0)	<0.0001
Other	10 (8.3)	22 (18.3)	0.036
BMI, kg/m^2, median (IQR)	25.5 (22-31)	25 (22-31)	0.98
Charlson Comorbidity Index Score, mean	4	5	0.23
Presence of sepsis*			
No sepsis	42 (35)	74 (61.7)	0.0001
Sepsis**	70 (58.3)	41 (34.2)	0.0003
Septic Shock***	8 (6.7)	5 (4.2)	0.57
Concomitant nephrotoxic drug			
IV contrast dye	43 (35.8)	45 (37.5)	0.89
Vasopressors	8 (6.7)	6 (5)	0.78
Loop diuretics	18 (15)	19 (15.8)	-
Other^	27 (22.5)	39 (32.5)	0.11
Highest vancomycin dose, mg/day, mean ± SD	3094 ± 851	2253 ± 658	<0.00001
Daily vancomycin dose ≥4g/day	20 (16.7)	0 (0)	<0.0001
Highest vancomycin trough during therapy+			
<15 mcg/ml	64 (53.3)	72 (60)	0.36
15-20 mcg/ml	38 (31.7)	29 (24.2)	0.25
>20 mcg/ml	18 (15)	19 (15.8)	-
ICU admission	54 (45)	26 (21.7)	0.0002
Baseline SCr, mg/dL, mean ± SD	0.87 ± 0.2	0.87 ± 0.2	0.98
Duration of combination therapy, days, median (IQR)	2 (2-3)	3 (2-5)	<0.00001

* Documented sepsis within 24 hours before or after antibiotic combination therapy initiation
** 2 of 4 SIRS criteria
*** At least 1 dose of vasopressor administered within 24 hours before or after initiation of combination therapy
^ Other nephrotoxic drugs: ACEi/ARB (new start), acyclovir, aminoglycosides, amphotericin B, calcineurin inhibitors, cyclosporine, NSAIDs, sulfamethoxazole/trimethoprim, tenofovir
+ Vancomycin levels were extrapolated if not a trough

Table 2. Incidence of AKI and AKI Staging

	Unmatched			Matched		
	VPT N=120 (%)	VC N=120 (%)	*P* value	VPT N=99 (%)	VC N=99 (%)	*P* value
AKI	21 (17.5)	4 (3.3)	0.0005	15 (15.2)	4 (4)	0.01
KDIGO Stage						
Stage 1	12 (10)	3 (2.5)	0.03	9 (9.1)	3 (3)	0.13
Stage 2	7 (5.8)	0 (0)	0.01	4 (4)	0 (0)	0.12
Stage 3	2 (1.7)	1 (0.8)	-	2 (2)	1 (1)	-

Table 3. Secondary Outcomes for All Patients

	Unmatched			Matched		
	VPT N=120	VC N=120	*P* value	VPT N=99	VC N=99	*P* value
Length of stay, days, median (IQR)	10 (6-17)	8 (5-13)	0.03	10 (6-19)	7.5 (4-12)	0.01
90-day mortality, n (%)	21 (17.5)	21 (17.5)	-	20 (20.2)	16 (16.2)	0.58
C. difficile infection up to 90 days, n (%)	6 (5)	2 (1.7)	0.28	5 (5.1)	2 (2)	0.44

Table 4. Secondary Outcomes for AKI Cohort

	Unmatched			Matched		
	VPT N=21	VC N=4	*P* value	VPT N=15	VC N=4	*P* value
Time to AKI, days, median (IQR)	3 (2-4)	4.5 (3-6)	0.16	3 (2-4)	4.5 (2-6)	0.22
Time to CKD w/in 90 days, n (%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-
HD need up to 1 year, n (%)	1 (0.8)	0 (0)	-	1 (0.7)	0 (0)	-

DISCUSSION

Nephrotoxicity is significantly greater with combination vancomycin and piperacillin-tazobactam compared to vancomycin and cefepime. This outcome may in part be influenced by differences in baseline characteristics between the study cohorts. Decisions to use these antibiotic combination therapies, especially vancomycin and piperacillin-tazobactam, should be accompanied by evaluation of other AKI risk factors in addition to close monitoring.

Larger, prospective studies are warranted to confirm the results of our study. In the meantime, based on these results, caution should be exercised when vancomycin and piperacillin-tazobactam are used in combination. Clinicians should minimize risk factors for acute kidney injury while patients remain on combination therapy, including avoiding concurrent nephrotoxins, maintaining adequate hydration, and carefully monitoring renal function and vancomycin levels. Additionally, antimicrobial stewardship programs should continue to utilize strategies to limit unnecessary initiation of vancomycin and antipseudomonal combination therapy, especially in patients with non-severe presentation.

LIMITATIONS

First, due to the retrospective nature of the study we were unable to demonstrate causality nor control for inherent biases associated with this type of study design. Second, as our study was conducted in two VA institutions, which largely consists of older male patients, the results may not be generalizable to other populations. Third, our study might also not be generalizable to patients with renal insufficiency, as we excluded patients with baseline renal insufficiency. There were differences in baseline characteristics between the two study groups. Our study attempted to overcome these limitations, however, by matching for potential confounding baseline characteristics including presence of liver disease, sepsis, ICU admission, and vancomycin dosing.

CONCLUSION

VPT combination therapy was associated with increased incidence of AKI compared to VC, though 90-day mortality and other outcomes were similar. Advising prescribers about potentially increased risk of AKI with VPT is a viable stewardship intervention.