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Characterizing The Nephrotoxicity of Vancomycin Combined With Piperacillin-Tazobactam or Cefepime In The Era of Extended-Infusion Dosing

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1. Abstract

1.1 Purpose

Vancomycin is a known cause of nephrotoxicity. The influence of concomitant administration of piperacillin-tazobactam or cefepime on development of Acute Kidney Injury [AKI] has not been firmly established. The objective of this study was to characterize and compare acute kidney injury associated with vancomycin plus either piperacillin-tazobactam or cefepime in the era of extended-infusion beta-lactams.

1.2 Design

This was a retrospective cohort study at a large academic medical center.

1.3 Subjects

The study assessed adult patients who received piperacillin-tazobactam/vancomycin [PT/V] or cefepime/vancomycin [C/V] initiated within 48 hours of each other and continued for ≥48 hours. Most patients received extended-infusion dosing of the beta-lactam.

1.4 Methods

Data were collected via chart review for included patients who were followed for up to 7 days after the start of combined therapy or 48 hours after discontinuation, whichever was shorter.

1.5 Main Outcome Measures

The primary endpoint was the incidence of nephrotoxicity defined using the Acute Kidney Injury Network criteria. Risk factors for AKI and time to onset of AKI were also evaluated.

1.6 Results

A total of 124 patients were included in the study, with 62 in each group. The incidence of AKI was higher with PT/V compared to C/V [37.1% vs 8.1%, p=0.0003]. When evaluated by multivariable analysis, the odds of developing AKI with PT/V were 6.1 times higher than with C/V after adjusting for the following risk factors: age, COPD, congestive heart failure, extended infusion beta-lactam, and more than 1 additional nephrotoxic agent. The proportion of patients AKI-free was significantly different between groups using a Kaplan Meier log rank test [p=0.0002].

1.7 Conclusion

PT/V was an independent risk factor for AKI. AKI associated with this antibiotic combination occurs as early as 48 hours of therapy. Contribution of extended-infusion dosing of cefepime could not be demonstrated.

2. Keywords: Acute Kidney Injury; Cefepime; Extended Infusion Dosing; Piperacillin-Tazobactam; Vancomycin

3. Introduction

Acute kidney injury [AKI] is deterioration in kidney function resulting from a functional or structural alteration to the kidney. AKI leads to increased length of stay, healthcare costs, duration of mechanical ventilation, and mortality [1].

Antibiotics as a drug class are commonly associated with AKI. Nephrotoxicity associated with vancomycin has long been documented in the literature [2]. Vancomycin is thought to cause AKI via Acute Tubular Necrosis [ATN] and has an incidence ranging from 1-42.5% [2]. Factors associated with increased risk of AKI with vancomycin include use of other nephrotoxic medications, comorbidities, higher vancomycin doses [>4g/day] and trough values >15 mg/dL. [2]. Beta-lactam associated AKI is thought to be due to acute interstitial nephritis [AIN] [3]. Of note, the package inserts for cefepime and piperacillin-tazobactam list the incidence of nephrotoxicity to be <1%. Recent literature has shown an increased risk of AKI when some beta-lactams are used in combination with vancomycin [4-11]. Piperacillin-Tazobactam/Vancomycin [PT/V] and Cefepime/Vancomycin [C/V] are both commonly used as empiric antibiotic regimens in the inpatient setting. The incidence of nephrotoxicity with these beta-lactams each paired with vancomycin is less defined.

Data exploring the influence of concomitant administration of various beta-lactams with vancomycin on the incidence of AKI are inconclusive. Studies comparing PT/V to vancomycin alone have uniformly identified greater risk of AKI with the combination [4-6]. However, analogous comparisons between C/V and PT/V have yielded inconsistent results [7-11].

The objective of this study was to characterize and compare acute kidney injury associated with vancomycin plus either piperacillin-tazobactam or cefepime in the era of extended-infusion beta-lactams.

4. Materials and Methods

This was a retrospective cohort study conducted at an 885-bed academic medical center. It was reviewed and approved by the institution's Investigational Review Board.

To be included in the study, patients received vancomycin and either piperacillin/tazobactam or cefepime initiated within 48 hours of each other and continued for at least 48 hours. Participants were also required to have a baseline serum creatinine obtained within 24 hours of admission and at least one vancomycin serum trough concentration. Patients with underlying renal insufficiency [CrCl <60 mL/min], structural kidney disease [renal cancer, transplant, or single kidney], or AKI prior to antibiotic initiation were excluded. Patients were also excluded if laboratory data such as serum creatinine was missing which precluded the ability to assess for AKI.

The electronic medical record system was utilized to generate a report of patients who received vancomycin plus either piperacillin-tazobactam or cefepime between April and August of 2015. These patients were screened in random order until a target of 62 patients in each group was achieved. Assuming a 35% incidence of AKI with PT/V and 20% absolute difference in the incidence of nephrotoxicity with PT/V compared to C/V, a sample size of 124 [62 patients in each group] was required to reach 80% power with an a priori significance level of 0.05. April to August 2015 was selected as the study period as this time frame encompassed use of both cefepime and piperacillin-tazobactam before a drug shortage limited use of piperacillin-tazobactam. However, because an insufficient number of PT/V patients were identified from the initial report [only 48 of target 62], a separate report listing patients who received PT/V during February and March of 2015 was obtained. These patients were assessed in reverse chronological order until the target sample size was attained.

The primary endpoint was the incidence of nephrotoxicity defined using the Acute Kidney Injury Network [AKIN] criteria: an increase in SCr of ≥ 0.3 mg/dL or > 50% from baseline within 48 hours or urine output < 0.5 mL/kg/hour for > 6 hours [13]. Since urine output is not well documented for patients outside of the ICU, urinary output criteria were only considered for patients in the ICU. Other outcomes analyzed included time from initiation of combination therapy to AKI and proportion of patients AKI-free. Patients were evaluated daily for 7 days after the start of combined therapy or 48 hours after discontinuation of antibiotics if given less than 7 days.

The following data elements were collected: demographic information, comorbid conditions, antibiotic doses, duration of beta-lactam infusion, serum creatinine, urine output, vancomycin trough concentrations, and receipt of other nephrotoxic agents. When collecting data on nephrotoxic agents, home medications as well as medications given during the evaluation period were recorded. To be classified as having received a nephrotoxic agent, the patient was required to have at least one dose charted during hospitalization prior to any AKI or take the nephrotoxic medication regularly prior to admission. Nephrotoxic agents were divided into high risk and low risk categories. High-risk agents included IV contrast, aminoglycosides, amphotericin, and scheduled NSAIDs. NSAIDs taken as needed, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers were considered low risk agents.

Results were analyzed with Pearson's chi square test or Fisher's exact test for categorical variables and a two-sample t-test for continuous variables. Logistic regression was used to identify differences among patients with or without AKI. To determine independent factors associated with AKI, a multivariable analysis was performed. Variables included in the analysis were those that were statistically significant in univariate comparisons [p<0.05]. A

Kaplan-Meier curve was constructed, and the log rank test was used to analyze time to AKI. Patients were censored at 7 days or at 48 hours after completion of study antibiotics, whichever occurred sooner. R Studio software was used for all analyses [14].

5. Results

Six-hundred and fifty patients identified as receiving either PT/V or C/V between April and August 2015 were screened in random order; 62 patients in the C/V group and 48 patients in the PT/V group met criteria to be included in the analysis. 93 patients receiving PT/V during February and March 2015 were screened to identify the remaining 14 PT/V patients to meet the desired sample size. Most patients who did not meet inclusion criteria did so because they were not on the combination of antibiotics for at least 48 hours. Figure 1 outlines how patients were selected for study inclusion.

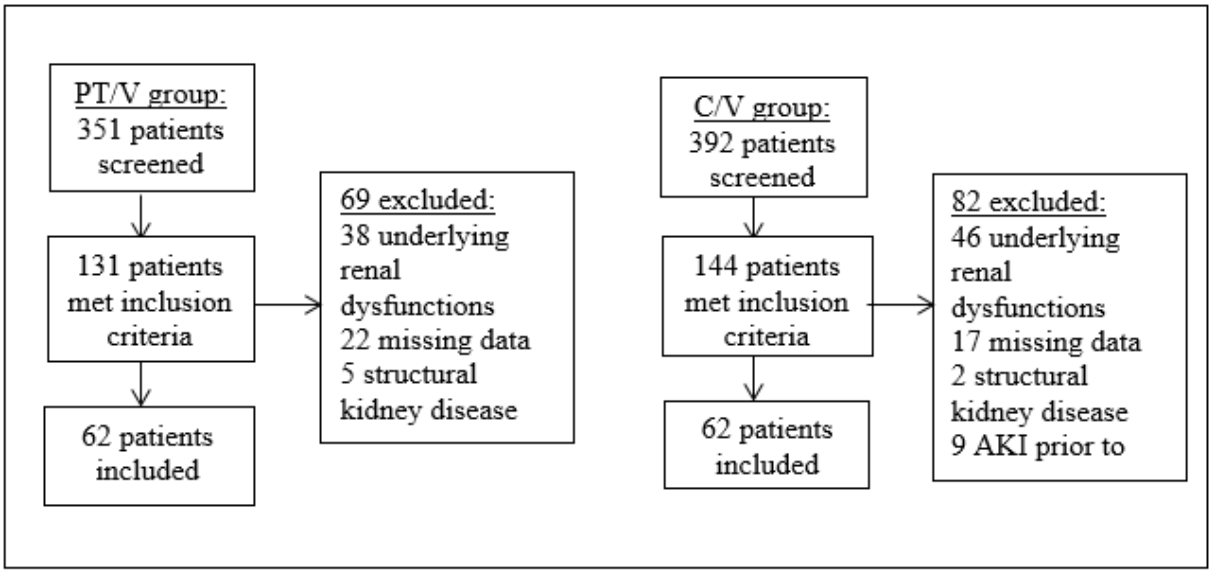

Figure 1: Schematic of the Patient Selection Process.

Baseline demographics were similar between groups [Table 1]. Patients in the C/V group were significantly older than patients in the PT/V group [59.0 vs 53.4 years, p=0.04]. The average admission serum creatinine was 0.81 mg/dL. Similar vancomycin exposure was noted between the groups as reflected in number of patients receiving > 4g/day and vancomycin trough > 15mg/L. All the patients in the PT/V group received extended infusion of the beta-lactam compared to 56.4% of C/V patients [p<0.0001]. Patients in the PT/V group received more than one nephrotoxic agent more frequently than those in the C/V group [40.3% vs 14.5%, p=0.003], but this difference was driven primarily by a greater number of patients in the PT/V group who received low-risk nephrotoxic medications [45.2% vs 27.4%].

	PT/V [n=62]	C/V [n=62]	p-value
Age in years, mean ± SD	53.4 ± 16.1	59.0 ± 14.2	0.04
Male, n [%]	33 [53.2]	37 [59.7]	0.59
Weight in kg, mean ± SD	80.8 ± 25.1	78.6 ± 23.5	0.62

Admission SCr in mg/dL, mean ± SD	0.81 ± 0.24	0.81 ± 0.25	0.94
Charlson Comorbidity Index, median [IQR]*	2 [1]	2 [2]	0.19
Comorbidities, n [%]			
HTN	33 [53.2]	24 [38.9]	1
Cancer	20 [32.3]	19 [30.6]	1
COPD	6 [9.7]	18 [29.0]	0.01
CHF	5 [8.1]	16 [25.8]	0.02
DM	20 [32.3]	15 [24.2]	0.42
MI	12 [19.4]	10 [16.1]	0.46
Service, n [%]			0.57
Medicine	15 [24.2]	15 [24.2]	
Surgery	15 [24.2]	9 [14.5]	
Hospitalist	10 [16.1]	9 [14.5]	
Oncology	10 [16.1]	14 [22.6]	
ICU	11 [17.7]	11 [17.7]	
Intermediate care	1 [1.6]	4 [6.5]	
Infection, n [%]			0.95
Pneumonia	24 [38.7]	28 [45.2]	
Sepsis	8 [12.9]	7 [11.2]	
Intra-abdominal	5 [8.1]	4 [6.5]	
Skin and soft tissue	11 [17.7]	7 [11.2]	
Urinary	2 [3.2]	4 [6.5]	
Bacteremia	2 [3.2]	2 [3.2]	
Bone/joint	5 [8.1]	3 [4.8]	
Neutropenic fever	3 [4.8]	4 [6.5]	
Multiple infections/unknown	2 [3.2]	3 [4.8]	
Days of concomitant therapy, mean ± SD	4.2 ± 2.2	3.9 ± 2.1	0.5
Extended infusion, n [%]	62 [100]	35 [56.4]	<0.0001
Vancomycin dose > 4g/day, n [%]	6 [9.7]	5 [8.0]	0.36
Vancomycin trough, n [%]			0.36
< 10 µg/mL	13 [20.9]	20 [32.3]	
10-20 µg/mL	42 [67.7]	36 [58.1]	
> 20 µg/mL	7 [11.3]	6 [9.7]	

Patients on other nephrotoxic agents, n [%]			
At least 1 high risk	37 [59.7]	31 [50]	0.37
At least 1 low risk	28 [45.2]	17 [27.4]	0.06
> 1 agent overall	25 [40.3]	9 [14.5]	0.003
Medicine included any general medicine floor service as well as gerontology and cardiology. Surgery included plastic, general, cardiothoracic, neurosurgery, orthopedic, urology, and ENT. Intensive care units [ICU] included medical, trauma, cardiovascular, and neurology.			

Table 1: Patient Characteristics.

Overall, 28 patients [22.5%] in the study experienced AKI. The primary endpoint, AKI, occurred significantly more often in the PT/V group than the C/V group [37.1% vs. 8.1%, p=0.0003]. In the 23 patients who experienced AKI in the PT/V group, median time [± IQR] from initiation of combination therapy to AKI was 2.2 ± 1.1 days. In the C/V group, 5 patients experienced AKI with a mean time to AKI of 1.2 ± 0.8 days [p=0.20]. In each group, 1 patient met the AKI definition based on decreased urinary output. No patients in the study required renal replacement therapy.

In a logistic regression analysis, the odds of developing AKI were 6.7 times higher in the PT/V group compared to the C/V group [95% CI 2.52-21.4]. Receiving extended infusion duration of the beta-lactam antibiotic [96.5% vs 72.9%, p=0.017] and receipt of PT/V [82.1% vs 40.6%, p=0.00026] were the only variables significantly different among patients with AKI compared to patients without AKI. In the multivariate model, PT/V was the only independent predictor of AKI [OR=4.57, 95% CI 1.56-16.8], as displayed in [Table 2]. A sensitivity analysis using multivariate regression including characteristics that were different between treatment groups showed similar results with PT/V being the only independent predictor of AKI [OR=6.1, 95% CI 1.73-28.5]. Another sensitivity analysis evaluating only patients who received an extended beta-lactam infusion [n=97] also demonstrated increased risk of AKI with PT/V [OR=4.57, 95% CI=1.56-16.8]. The Kaplan-Meier curve for time to AKI is shown in Figure 2. The difference in AKI-free survival between treatments was significant [p= 0.0002]. The curves appear to separate at 24-48 hours of therapy with PT/V.

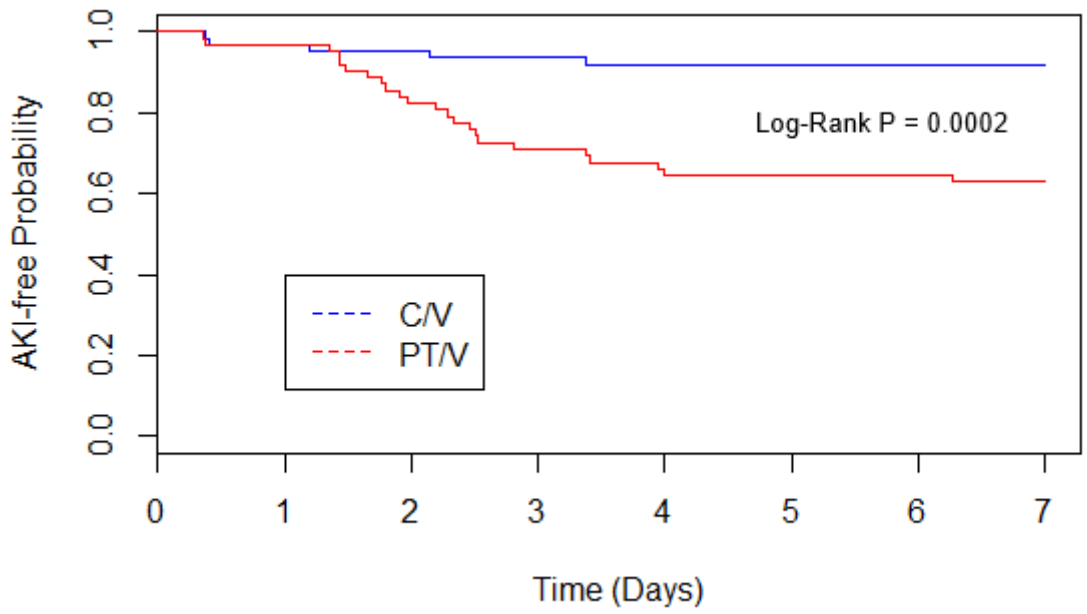

Figure 2: Time to Acute Kidney Injury.

	Univariate Analysis		Multivariate Analysis	
Variable	**OR [95% CI]**	**p-value**	**OR [95% CI]**	**p-value**
PT/V treatment	6.72 [2.52-21.39]	0.0004	4.57 [1.56-16.81]	0.01
Extended infusion beta lactam	10.03 [1.97-183.38]	0.027	3.35 [0.46-67.82]	0.29
Multiple nephrotoxic agents [1]	2.05 [0.82-4.99]	0.11		
Age [1]	0.98 [0.96-1.01	0.46		
Congestive heart failure [1]	1.08 [0.33-3.12]	0.88		
Chronic obstructive pulmonary disease [1]	0.88 [0.27-2.47]	0.82		
[1] Included in sensitivity analysis				

Table 2: Factors Associated with AKI.

6. Discussion

The results of this investigation help to solidify our understanding of AKI associated with vancomycin in combination with common broad-spectrum beta-lactam antibiotics. The risk of AKI is greater with PT/V compared to C/V, and this finding is consistent with results of previous studies. This investigation further characterizes AKI associated with PT/V by

illustrating a surprisingly early onset. Furthermore, an association between AKI and extended-infusion dosing of cefepime could not be demonstrated.

Previously published retrospective studies had similar reported incidences of AKI compared to our study. A study published in 2014 by Gomes et al. found the incidence of nephrotoxicity was significantly higher in the PT/V group compared to the C/V group in their propensity matched cohort [36.4% vs 10.9%; odds ratio 5.67 [95% CI 1.66-19.33], p=0.003] [7]. In 2017, Navalkele, et al. published a study showing the incidence of AKI was 29% in the PT/V group vs 11% in the C/V group [hazard ratio=4.27, 95% CI 2.73–6.68] [8]. Both studies concluded that piperacillin-tazobactam with vancomycin is independently associated with AKI.

More recently, a prospective, multicenter, observational study was published evaluating AKI with PT/V compared to vancomycin in combination with cefepime or meropenem [9]. This study concluded that the incidence of AKI was 6.7 times more likely with PT/V use verses the comparator group [29.8% versus 8.8%, P < 0.001].

However, not all studies that examined this issue reached the same conclusion. In a study of critically ill patients, Hammond et al. assessed the incidence of AKI up to 72 hours after completing therapy with vancomycin plus either piperacillin-tazobactam or cefepime.[10] This study reported no difference in the rate of AKI with PT/V compared to C/V [32.7% vs 28.8%, p=0.761].

Two meta-analyses evaluated the risk of AKI with PT/V compared to other beta-lactams combined with vancomycin. In the first analysis, Giuliano and colleagues evaluated 15 observational cohort studies which included 3258 adult patients. Relative to other beta-lactams, PT/V was associated with AKI [OR=3.649, 95% CI 2.157-6.174] [11]. In the second meta-analysis, Hammond and colleagues evaluated 14 observational studies totaling 3549 patients and found similar results [OR=3.12, 95% CI 2.04–4.78] [12]. The "other" beta lactam in these studies was most often cefepime, but a fewer number included meropenem. Except for a single study in critically ill patients, the findings of previously published studies, including these meta-analyses, are consistent with the results of our study.

During the study period, the institution's routine infusion time for cefepime was changed from 30 minutes to 4 hours. Therefore, the C/V group contained patients who received cefepime by both standard and extended infusion. When accounted for in the multivariate analysis, infusion time was not found to contribute to the difference in AKI between the groups. The results of this study are consistent with a recent study where Cotner and colleagues evaluated the impact of beta lactam infusion time on AKI [15]. This study concluded that prolonged and intermittent infusions of beta lactams had similar rates of AKI [21.6% vs 18.6%, p=0.1] and that prolonged infusion duration was not an independent predictor of AKI. The study did find that piperacillin-tazobactam therapy was an independent predictor of AKI.

This study is not without limitations. Since urinary output documentation is not always reliable outside of our intensive care units, only patients in the ICU were assessed for AKI based on urinary output, so an AKI event in non-ICU patients could have been missed. It is unlikely that there was bias introduced from prescribers choosing between piperacillin-tazobactam and cefepime as there were no treatment algorithms in place that would systematically recommend the choice of one agent over the other. In addition, *Pseudomonas aeruginosa* susceptibility on the institution's antibiogram was similar for both beta-lactams.

This study does not offer any explanation as to the mechanism behind the increased incidence of AKI seen with PT/V. Vancomycin is believed to cause AKI via ATN while beta lactams can

cause AIN [4]. These different mechanisms may act synergistically when vancomycin and beta lactams are combined. Limited data exists comparing the risk of AKI with other beta lactams as monotherapy. Flynt et al. compared the risk of AKI with nafcillin to cefazolin in patients with MSSA bacteremia and found nafcillin had a significantly higher risk of nephrotoxicity compared to cefazolin [33% vs 13%, p=0.007] [16]. Nafcillin was an independent predictor of AKI [OR 2.74; 95% CI 1.1–6.6].

While the results of this study are consistent with most previously published results, the contribution of piperacillin-tazobactam to the risk of nephrotoxicity is still not conclusive. Almost all previously published studies, including this one, are short-term, observational, cohort studies. Further prospective research is needed to determine the true incidence of nephrotoxicity with these antibiotics as well as long-term clinical outcomes for patients who develop nephrotoxicity. In the meantime, clinicians are advised to proactively consider the potential for AKI when prescribing PT/V. Evaluation of other risk factors for AKI should be incorporated into clinical decision making. Such patients may be more safely treated with a different beta-lactam or an alternative anti-MRSA agent.

7. Conclusion

This investigation found that adult patients without pre-existing renal dysfunction treated with ≥ 48 hours of PT/V have a higher risk of AKI compared to patients receiving C/V. AKI associated with PT/V occurs as early as 48 hours of therapy, and the use of extended-infusion dosing is not likely to be a significant contributor. Prescribers are advised to consider the risk of AKI associated with PT/V when choosing antibacterial therapy.

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