Comparison of Acute Kidney Injury During Treatment with Vancomycin in Combination with Piperacillin-Tazobactam or Cefepime

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Study Objective To evaluate the observed incidence of acute kidney injury (AKI) in adult patients receiving either piperacillin-tazobactam and vancomycin or cefepime-vancomycin for more than 48 hours.

Design Retrospective matched cohort.

Setting Large academic medical center.

Patients Adult patients without preexisting renal dysfunction admitted over an 8-month time period who received either the combination of piperacillin-tazobactam and vancomycin or cefepime-vancomycin for more than 48 hours were evaluated for AKI, defined by the Acute Kidney Injury Network criteria.

Measurements and Main Results A total of 224 patients receiving either antimicrobial combination were evaluated for AKI. The incidence of AKI was significantly higher in the piperacillin-tazobactam and vancomycin group (34.8%) compared with the cefepime-vancomycin group (12.5%) in the unmatched analysis ($p<0.0001$). After adjusting for potential sources of bias through propensity score matched pairs and conditional logistic regression, piperacillin-tazobactam and vancomycin combination therapy ($p=0.003$) was an independent predictor of AKI. There were no significant differences in time to AKI or hospital length of stay between groups.

Conclusions The results of this study suggest that there may be an association between piperacillin-tazobactam and vancomycin combination therapy and increased incidence of AKI.

Key Words vancomycin, piperacillin-tazobactam, cefepime, nephrotoxicity, acute kidney injury.

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In the United States, vancomycin and antipseudomonal β-lactam antibiotics, such as piperacillin-tazobactam, are commonly prescribed agents in hospitalized patients.[1, 2] These antibiotics are typically used as empirical combination therapy in patients who are at risk of infections caused by drug-resistant pathogens. Many of these antibiotics including vancomycin, aminoglycosides, and certain β-lactams have been reported to cause drug-induced nephrotoxicity (DIN), a subtype of acute kidney injury (AKI).[3–5]

Risk factors, such as preexisting renal dysfunction, diabetes, hypertension, hypotension, malignancy, sepsis, hypoalbuminemia, volume depletion, human immunodeficiency virus and

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acquired immunodeficiency syndrome, and advanced age, predispose patients to drug-induced AKI.[6] Patients receiving contrast media, nonsteroidal antiinflammatory drugs (NSAIDs), amphotericin B, acyclovir, angiotensin-converting enzyme inhibitors (ACE-Is), chemotherapeutic agents, or vasopressors are also at increased risk for AKI.[7] The presence of multiple risk factors increases the risk of AKI synergistically.[7]

The risk factors and incidence of vancomycin-induced AKI are well described in the medical literature. However, reports suggesting that piperacillin-tazobactam may be associated with higher rates of nephrotoxicity when used as monotherapy and in combination with vancomycin are becoming more prevalent.[4, 8–18] To our knowledge, no published studies have examined the rate of nephrotoxicity when cefepime is combined with vancomycin across multiple disease states.

The purpose of this study was to compare the observed incidence of AKI between two empirical combination antibiotic regimens: piperacillin-tazobactam and vancomycin and cefepime-vancomycin in adult patients without documented preexisting renal insufficiency.

Methods

Study Setting

The University of Florida (UF) Health Jacksonville is a 695-bed tertiary academic hospital with teaching (internal medicine) and nonteaching (hospitalist) inpatient services, a level-one trauma center, and adult and pediatric intensive care units. This study was approved by the UF Health Science Center Jacksonville institutional review board.

Study Design and Population

This was a retrospective matched-cohort study of patients admitted to UF Health Jacksonville between January 21, 2012, and October 15, 2012. Patients received either a combination of piperacillin-tazobactam and vancomycin or cefepime-vancomycin. During the study period, no treatment algorithms were in place that would bias selection of piperacillin-tazobactam or cefepime for the included indications. Also, *Pseudomonas aeruginosa* blood and respiratory isolates from 2011 were reported in the institution's antibiogram as 81% (minimum inhibitory concentration [MIC] 16 μg/ml or lower) and 86.5% (MIC 8 μg/ml or lower) susceptible for piperacillin-tazobactam and cefepime, respectively. For indications that may have required anaerobic coverage, the addition of metronidazole to the cefepime-vancomycin combination was left to the discretion of the prescriber. Piperacillin-tazobactam (Pfizer Inc., Philadelphia, PA) was utilized for all doses during the study period, but multiple generic products were used for cefepime and vancomycin therapy depending on availability. A typical empirical dose of piperacillin-tazobactam was 4.5 g administered intravenously every 8 hours and 2 g every 8–12 hours for cefepime. Per institutional protocol, most adult patients received the first dose of piperacillin-tazobactam over 30 minutes, with all subsequent doses administered over 4 hours. Cefepime was administered as either a 3-hour extended infusion or as an intermittent infusion over 30 minutes. Vancomycin dosing was typically left to the discretion of the prescribers from teaching services, but clinical pharmacists were available during all hospital hours for assistance in dosing and monitoring. Additionally, a pharmacist-managed pharmacokinetics consultation service was available to nonteaching services for vancomycin management.

Patients were included in the study if they were 18 years old or older, had a baseline serum creatinine (S_{cr}) within 24 hours of admission and at least one vancomycin trough level, and had received treatment with piperacillin-tazobactam and vancomycin or cefepime-vancomycin for at least 48 hours during admission, and the combination of these agents was initiated no more than 48 hours apart. Patients were excluded if they were currently receiving dialysis, had a history of chronic kidney disease (stage III or higher) or structural kidney disease (e.g., one kidney, kidney transplant, kidney tumor), or renal insufficiency (creatinine clearance [Cl_{cr}] less than 60 ml/min at admission). Other reasons for exclusion were current pregnancy, incarceration, treatment with investigational medications, or treatment with more than one dose of intermittent (over 30 minutes) piperacillin-tazobactam infusion. To limit antimicrobial selection bias based on indication or pharmacokinetic profile, patients were also excluded if they had febrile neutropenia or were being treated for meningitis.

Study End Points

The primary end point was the difference in rates of AKI for patients treated with either the

antimicrobial combination therapy of piperacillin-tazobactam and vancomycin or cefepime-vancomycin. Acute Kidney Injury Network (AKIN) guidelines were used to define AKI occurring during therapy or within 72 hours after combination therapy was discontinued.[19] Secondary study end points for each group included time to AKI from initiation of combination therapy and hospital length of stay (LOS).

Data Collection

Medical and laboratory data were extracted from electronic medical records. Data collected included age, gender, weight, Charlson Comorbidity Index, antibiotic allergies, previous β-lactam antibiotics or vancomycin within 90 days of admission (when documented), concomitant nephrotoxic medications (i.e., aminoglycoside antibiotics, amphotericin B, acyclovir, NSAIDs, ACE-Is, loop diuretics, intravenous [IV] contrast, or IV chemotherapy), hospital unit (intensive care unit [ICU] or non-ICU), service (internal medicine, hospitalist, or specialty) at start of antibiotic therapy, indications for antibiotic therapy, pharmacy pharmacokinetic consultation, nephrology service consultation, and AKI resolution status (resolved, insult still present, dialysis required during insult). Hospital LOS, infection-related LOS, and disposition (death, long-term care, home) were also collected. Infection-related LOS was defined as the number of days from the start of antibiotics for the specified indication to either the discontinuation of antibiotics or hospital discharge.

Data describing vancomycin, cefepime, and piperacillin-tazobactam treatment were collected from the initial course of either piperacillin-tazobactam and vancomycin or cefepime-vancomycin during the hospitalization. Antibiotic days were defined as receipt of at least one dose of antibiotic on a given day. The highest vancomycin trough prior to AKI diagnosis was also collected. Vancomycin troughs that were not drawn appropriately (i.e., more than 2 hours prior to the next scheduled vancomycin administration) were excluded from the analysis.

Within 24 hours of admission, S_{cr} and estimated Cl_{cr} calculated by the Cockcroft-Gault formula were recorded as baseline values. Both S_{cr} and Cl_{cr} were also collected at the initiation of piperacillin-tazobactam and vancomycin or cefepime-vancomycin therapy, up to 72 hours after antibiotic discontinuation and again at discharge. Patients who developed AKI during antibiotic therapy or within the period lasting 72 hours after discontinuation of antibiotics were staged according to the AKIN criteria. The total number of days of AKI and the time to AKI (days from initiation of antibiotics to AKI) were assessed using the start of AKI and antibiotics as day 0.

Statistical Analysis, Propensity Score, Case-Match Procedure

In the full sample, comparisons for demographic, baseline characteristics, the time to AKI, and LOS between the two groups were assessed using the nonparametric Wilcoxon rank sum test for continuous data and the Pearson χ^2 test or Fisher exact tests for categorical data including the incidence of AKI. A p value of 0.05 or less was considered significant. A sample size of 112 patients per group was required to achieve a statistical power of 80% based on estimates of a 25% rate of AKI in the piperacillin-tazobactam and vancomycin group and 10% in the cefepime-vancomycin group.[13] Ten percent of the collected data was reviewed by a coinvestigator for interrater reliability, resulting in 100% agreement.

Because the rationale for assigning patients to either regimen was unknown, the comparison between these two regimens was subject to potential bias. To control for this potential bias and balance observed covariates among the two groups, propensity scores were estimated. Using a logistic regression model, the predicted probability of receiving piperacillin-tazobactam and vancomycin, (i.e., the propensity score) was estimated for each individual in the data set.[20] Patients in the piperacillin-tazobactam and vancomycin group were matched to those in the cefepime-vancomycin group who had comparable propensity scores. The matching process was completed using an SAS macro that uses a *greedy matching* algorithm based on 5–1 digit matching.[20, 21] Once a match was made, the individuals were not resampled. For the matched analysis, differences between matched pairs were assessed using the nonparametric signed rank test for continuous data and the McNemar test for binary data or the Bowker test of symmetry, for categorical data with more than two levels. Conditional logistic regression analysis was used on the matched data to determine whether the presence of AKI is associated with the treatment adjusting for baseline variables such as receipt of contrast media and number of contrast doses, concomitant nephrotoxic agents (IV contrast

agents, NSAIDs, aminoglycosides, and ACE-I), initial vancomycin troughs, and vancomycin duration. Best subset selection was used to determine the best predictive model among the baseline predictors. This approach uses the likelihood score statistic and fits all one through six-variable models. Although variables may be correlated, looking at the best models in this way allows us to determine if there is multicollinearity. All statistical analyses were run using SAS v.9.3 for Windows.

Results

Clinical Characteristics of the Cohort

In total, records from 643 patients were reviewed until data on 224 qualifying patients were collected (112 patients each for piperacillin-tazobactam and vancomycin and cefepime-vancomycin). Figure 1 lists the reasons for exclusion. Overall, patients who received the piperacillin-tazobactam and vancomycin combination were slightly older and had an overall higher mean body weight than patients in the cefepime-vancomycin group. Table 1 summarizes the other baseline demographic characteristics and antibiotic indications. Patients in the piperacillin-tazobactam and vancomycin group were less likely to be admitted to the ICU compared with the cefepime-vancomycin group (34.8% vs 53.6%, p=0.005). The initial vancomycin trough was similar between groups with a mean of 14.1 mg/L (SD = 8.09 mg/L) and 13.06 mg/L (SD = 6.08 mg/L) in the piperacillin-tazobactam and vancomycin and cefepime-vancomycin groups, respectively (p=0.58). There were more pharmacist-managed pharmacokinetics consultations for patients in the piperacillin-tazobactam and vancomycin group compared with patients in the cefepime-vancomycin group during the study period (40% vs 17%, respectively, p=0.0001). No statistically significant differences were found between each concomitant nephrotoxic agent (e.g., ACE-I, IV contrast, amphotericin, acyclovir, chemotherapy, or aminoglycosides) with the exception of NSAIDs (piperacillin-tazobactam and vancomycin 10.7% vs 22.3% cefepime-vancomycin, p=0.019). Between the piperacillin-tazobactam and vancomycin and the cefepime-vancomycin groups, no differences were found in mean LOS (18.5 vs 25.2 days, p=0.2) and infection-related LOS (13.1 days in both groups; p=0.70). Mean days of antimicrobial therapy were significantly higher in the piperacillin-tazobactam and vancomycin group than in the cefepime-vancomycin group (7.1 vs 6.7, respectively, p=0.003) before propensity score matching was conducted.

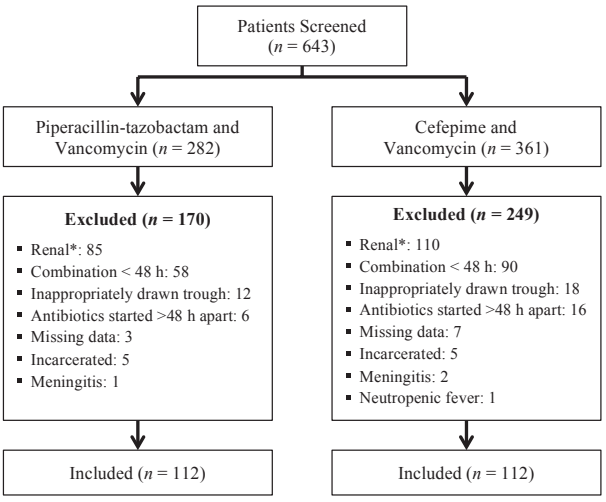

Figure 1. Study design. *Receiving dialysis, documented history of chronic kidney disease (≥ Stage III), structural kidney disease (e.g. one kidney, kidney transplant, kidney tumor), documented renal insufficiency (Cl_{cr} < 60 mL/min)

For unmatched data, the incidence of AKI was significantly higher in the piperacillin-tazobactam and vancomycin group (34.8%) compared with the cefepime-vancomycin group (12.5%) (odds ratio [OR] 3.74, 95% confidence interval [CI] 1.89–7.39, p<0.0001). The mean highest vancomycin trough prior to AKI was 22.6 mg/L (SD = 12.8 mg/L) in the piperacillin-tazobactam/vancomycin group and 24.3 mg/L (SD = 12.6 mg/L) in the cefepime-vancomycin group (p=0.52, Table 2). In the piperacillin-tazobactam and vancomycin group, 23 of 39 patients (59.0%) who developed AKI still had an insult present at discharge, compared with 11 of 14 patients (78.6%) in the cefepime-vancomycin group (p=0.190). Table 2 summarizes the severity and characteristics of the AKI.

Incidence of AKI, Propensity Score Matched Analysis

Overall, 55 pairs (49.1%) of patients were matched on propensity scores that were estimated using age, weight, S_{cr}, and estimated Cl_{cr} at both baseline and at initiation of antibiotics, admission unit, admission service, comorbidities, Charlson Comorbidity Index, antibiotic allergies, and indication. After matching, no significant differences were noted between the two groups with respect to the baseline covariates used to

Table 1. Comparison of clinical characteristics and outcomes in unmatched and matched pair analysis

	Unmatched data			Matched-pair analysis		
Characteristics	TZP-VAN (n=112)	FEP-VAN (n=112)	p	TZP-VAN (n=55)	FEP-VAN (n=55)	p
Age, yrs[a]	52.42 ± 13.91	50.37 ± 14.27	0.344[b]	51.47 ± 13.56	52.07 ± 13.97	0.875[b]
Male sex	66 (58.9)	64 (57.1)	0.787[c]	24 (43.6)	26 (47.3)	0.834[c]
Weight, kg[a]	91.54 ± 26.33	83.15 ± 27.76	0.004[b]	89.14 ± 23.88	85.75 ± 26.89	0.467[b]
Baseline S_{cr}, mg/dl[a]	0.79 ± 0.24	0.79 ± 0.25	0.934[b]	0.78 ± 0.22	0.74 ± 0.22	0.338[b]
Estimated Cl_{cr} at baseline, ml/min[a]	141.61 ± 58.32	130.40 ± 58.76	0.077[b]	139.71 ± 56.06	143.82 ± 74.30	0.693[b]
S_{cr} at start of antibiotics[a]	0.79 ± 0.24	0.74 ± 0.22	0.413[b]	0.75 ± 0.21	0.74 ± 0.22	0.776[b]
Estimated Cl_{cr} at antibiotic start, ml/min[a]	142.41 ± 58.90	142.45 ± 87.39	0.480[b]	143.84 ± 56.16	137.12 ± 58.77	0.894[b]
Charlson Comorbidity Index, age factored in[a]	2.96 ± 2.60	3.00 ± 2.70	0.997[b]	2.49 ± 2.20	3.05 ± 2.13	0.253[b]
Admission service						
Hospitalist	52 (46.4)	22 (19.6)	0.0001[c]	17 (30.9)	16 (29.1)	0.911[d]
Internal medicine	16 (14.3)	26 (23.2)		12 (21.8)	15 (27.3)	
Other	44 (39.3)	64 (57.1)		26 (47.3)	24 (43.6)	
Admission unit			0.005[c]			1.000[c]
ICU	39 (34.8)	60 (53.6)		22 (40.0)	23 (41.8)	
Non-ICU	73 (65.2)	52 (46.4)		33 (60.0)	32 (58.2)	
ICU ever during admission	52 (46.4)	72 (64.3)	0.009[c]	29 (52.7)	29 (52.7)	1.000[c]
Antibiotic allergies	4 (3.6)	8 (7.1)	0.223[c]	4 (7.3)	3 (5.5)	1.000[c]
Comorbidities						
Liver disease	15 (13.4)	10 (8.9)	0.289[c]	5 (9.1)	7 (12.7)	0.727[c]
Diabetes mellitus	43 (38.4)	25 (22.3)	0.009[c]	18 (32.7)	17 (30.9)	1.000[c]
Heart failure (NYHA I to IV)	10 (8.9)	13 (11.6)	0.509[c]	4 (7.3)	7 (12.7)	0.508[c]
CVD	34 (30.4)	26 (23.2)	0.227[c]	13 (23.6)	17 (30.9)	0.503[c]
Hypertension	66 (58.9)	53 (47.3)	0.081[c]	29 (52.7)	31 (56.4)	0.845[c]
COPD	24 (21.4)	19 (17.0)	0.396[c]	7 (12.7)	10 (18.2)	0.607[c]
HIV/AIDS	4 (3.6)	13 (11.6)	0.023[c]	3 (5.5)	4 (7.3)	1.000[c]
Malignancy	20 (17.9)	29 (25.9)	0.146[c]	11 (20.0)	14 (25.5)	0.678[c]
Other comorbidities	58 (51.8)	54 (48.2)	0.593[c]	23 (41.8)	30 (54.6)	0.189[c]
Concomitant nephrotoxic drugs						
Contrast	47 (42.0)	51 (45.5)	0.590[c]	19 (34.6)	18 (32.7)	1.000[c]
NSAID	12 (10.7)	25 (22.3)	0.019[c]	10 (18.2)	7 (12.7)	0.581[c]
ACE inhibitor	51 (45.5)	39 (34.8)	0.102[c]	21 (32.2)	22 (40.0)	1.000[c]
Aminoglycosides	7 (6.3)	11 (9.8)	0.326[c]	4 (7.3)	5 (9.1)	1.000[c]
Antibiotic indication						
Bacteremia	8 (7.1)	5 (4.5)	0.391[c]	3 (5.5)	4 (7.3)	1.000[c]
cSSTI	27 (24.1)	20 (17.9)	0.251[c]	11 (20.0)	11 (20.0)	1.000[c]
Respiratory tract infection	37 (33.0)	40 (35.7)	0.673[c]	19 (34.6)	19 (34.6)	1.000[c]
Intra-abdominal infection	11 (9.8)	3 (2.7)	0.027[c]	2 (3.6)	2 (3.6)	1.000[c]
Urinary tract infection	3 (2.7)	6 (5.4)	0.499[d]	2 (3.6)	2 (3.6)	1.000[c]
Empirical therapy	26 (23.2)	39 (34.8)	0.056[c]	17 (30.9)	17 (30.9)	1.000[c]
Other indications/infections	9 (8.0)	9 (8.0)	1.00[d]	5 (9.1)	5 (9.1)	1.000[c]

Data are number (%) unless otherwise indicated. ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; Cl_{cr} = creatinine clearance; cSSTI = complicated skin and soft tissue infection; FEP-VAN = cefepime and vancomycin combination; ICU = intensive care unit; NSAID = nonsteroidal antiinflammatory drug; NYHA = New York Heart Association; S_{cr} = serum creatinine; TZP-VAN = piperacillin-tazobactam and vancomycin combination.

[a]Mean ± SD.

[b]Signed rank test.

[c]McNemar test.

[d]Bowker test of symmetry.

calculate the propensity scores. Baseline characteristics for the propensity score matched pairs are shown in Table 1. In this analysis, the difference in the incidence of AKI was significantly higher in patients receiving piperacillin-tazobactam and vancomycin (36.4% vs 10.9%, p=0.003). Additional baseline variables were assessed for the matched-pair analysis including

Table 2. Prevalence and duration of acute kidney injury (unmatched data)

	TZP-VAN (n=39)	FEP-VAN (n=14)	p
Highest VAN trough prior to AKI, mg/L	22.6	24.3	0.52[a]
In ICU at AKI onset, no. (%)	11 (28.2)	9 (64.3)	0.017[b]
Days to AKI from combination start, mean	4.97 ± 3.1	4.85 ± 2.9	0.975[a]
AKIN stage, no. (%)			
I	25 (64.1)	6 (42.9)	0.049[c]
II	3 (7.7)	5 (35.7)	
III	11 (28.2)	3 (21.4)	
Total days of AKI, mean	7.6 ± 6.8	10.6 ± 14.8	0.626[a]
Outcome of AKI at discharge			
Resolved, no. (%)	16 (41.0)	3 (21.4)	0.190[c]
Insult still present, no. (%)	23 (59.0)	11 (78.6)	
Dialysis required, no. (%)	0 (0.0)	1 (7.1)	1.00[c]
Renal consult, no. (%)	6 (15.4)	4 (28.6)	0.426[c]

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; FEP-VAN = cefepime-vancomycin combination; ICU = intensive care unit; TZP-VAN = piperacillin-tazobactam and vancomycin combination.
[a]Wilcoxon rank sum test.
[b]Pearson χ^2 test.
[c]Fisher exact test.

receipt of contrast media and number of contrast doses, concomitant nephrotoxic agents (IV contrast agents, NSAIDs, aminoglycosides, and ACE-Is), initial vancomycin trough, and vancomycin duration. Receipt of piperacillin-tazobactam and vancomycin combination therapy was determined to be an independent predictor of AKI in the matched-pair sample.

Using best subset selection, the "best" model selected was the model including only treatment (p=0.006) as a significant predictor. The odds of AKI for the piperacillin-tazobactam and vancomycin group were 5.67 times greater than for the cefepime-vancomycin group (OR 5.67, 95% CI 1.66–19.33). The residual score statistic (residual χ^2 = 5.1284 with 8 degrees of freedom and p=0.744) indicates an adequate fit. The overall χ^2 for the best six-variable model was 12.3. That is, adding five additional variables resulted in a score χ^2 improvement of only 2.5, which does not reach significance level for a single variable (3.84). Thus there was no evidence that a significant predictor was omitted in the variable selection process.

Discussion

Although vancomycin-induced AKI is a known drug-related adverse effect, the incidence rates of AKI when this agent is used in combination with piperacillin-tazobactam or cefepime are not well studied. In our study, the incidence of AKI was significantly greater with the combination of piperacillin-tazobactam and vancomycin than with cefepime-vancomycin. To our knowledge, this evaluation provides the first published evidence of a difference in rates of AKI between these two common antibiotic treatment regimens when compared across multiple disease states.

In a study evaluating diabetic patients being treated for osteomyelitis, piperacillin-tazobactam and vancomycin combination therapy was not determined to be a statistically significant predictor of AKI compared with cefepime-vancomycin combinations (29.3% vs 13.3%, p=0.099).[16] One report[13] described increased rates of AKI in adult patients receiving vancomycin monotherapy (4.9%) compared with piperacillin-tazobactam monotherapy (11.1%, p=0.0241) or the combination of vancomycin and piperacillin-tazobactam (18.6%, p<0.001). Similarly, a higher rate of AKI was observed when vancomycin was used in combination with piperacillin-tazobactam than with vancomycin monotherapy in surgical intensive care unit patients (49.3% vs 8.9%, p≤0.001).[15]

In comparison with the previously mentioned studies, our study compared the incidence of AKI between two common β-lactam and vancomycin combinations utilized for empirical therapy in hospitalized patients. In an attempt to account for potential confounding by indication, propensity score matching was used to adjust for baseline variables, which may have influenced choice of therapy (e.g., admission unit, prescribing service, indications for antimicrobial therapy). The ORs for the unmatched (OR 3.74, 95% CI 1.89–7.39) and matched analyses (OR 5.67, 95% CI 1.66–19.33) are similar, suggesting the association is not due to confounding. These additional analyses confirmed the unadjusted results: The use of piperacillin-tazobactam and vancomycin in combination was still associated with a significantly higher incidence of AKI compared with the cefepime-vancomycin combination regimen. Piperacillin-tazobactam and vancomycin combination therapy was an independent predictor for the development of AKI, whereas other nephrotoxic medications were not associated with AKI. Although the days to AKI from start of combination antibiotic therapy were similar for patients in each group, patients treated with piperacillin-tazobactam and vancomycin trended toward a shorter duration

of AKI. This may be attributed to the larger majority of patients treated with piperacillin-tazobactam and vancomycin combinations that were classified as stage I according to the AKIN criteria compared with those treated with cefepime combinations (64.1% vs 42.9%). Upon discharge from the hospital, it is uncertain if patients had resolution of their AKI or experienced long-term sequelae because follow-up data were not collected.

Animal and human studies suggest vancomycin-induced nephrotoxicity occurs through destruction of glomeruli and accumulation in the proximal renal tubule leading to cellular necrosis.[4, 8, 22–24] Penicillins, including semisynthetic agents, have been reported to cause AKI through acute interstitial nephritis (AIN).[25, 26] Piperacillin-tazobactam has been implicated in causing AIN in at least six case reports, whereas there are no case reports of cefepime inducing AIN.[27–32] Earlier cephalosporin generations have also been linked to AIN, but literature on the newer cephalosporin generations is limited.[33] A plausible explanation for suspected lower rates of AKI with newer cephalosporin generations may be attributed to their chemical structure. Cefepime, a fourth-generation cephalosporin, is composed of different side chains compared with earlier generation cephalosporins that have similar chemical structures to aminopenicillins.[34] Our study did not find any statistically significant differences in high initial vancomycin trough or receipt of other nephrotoxic agents between treatment groups. This may suggest that the reason for the higher rate of AKI seen in this study could be linked to the use of piperacillin-tazobactam. The exact mechanism of action underlying the association between AKI and combination piperacillin-tazobactam and vancomycin is unknown. We hypothesize that the two proposed mechanisms of AKI associated with these antimicrobial agents (i.e., interstitial nephritis and direct cellular necrosis) may be augmenting one another; however, additional studies are needed to validate this hypothesis.

This study had several limitations. The data were retrospectively extracted in a nonblinded manner from the electronic health record, and accurate documentation was assumed. Through the use of propensity score methodology, we were able to balance a large number of baseline covariates successfully; however, there is a possibility of residual confounding by unobserved covariates. Data were not collected for all risk factors that predispose patients to drug-induced AKI, such as treatment with vasopressors or the presence of hypotension, sepsis, hypoalbuminemia, volume depletion, or high severity illness scores. Urine eosinophils or data from kidney biopsies were also not collected to classify the type of AKI (e.g., AIN vs direct nephrotoxicity). Also, the variations in the multiple generic products used for cefepime and vancomycin therapy may have influenced the incidence of AKI. Although we included most comorbidities, patients with baseline renal insufficiency or chronic kidney disease were excluded from this study. The retrospective design of the study makes it difficult to differentiate whether the patient's renal function was declining because of the combination therapy or a natural progression of disease processes. Although a statistical difference in baseline characteristic of diabetes with more patients in the piperacillin-tazobactam and vancomycin group was observed, mean baseline S_{cr} was identical in both groups. A multicenter prospective study should be conducted to confirm these results.

In conclusion, the present study suggests an increase in the risk of developing AKI with piperacillin-tazobactam and vancomycin combination therapy when compared with cefepime-vancomycin combination therapy. The mechanism by which combination piperacillin-tazobactam and vancomycin may increase the development of AKI remains to be fully understood. Although our study demonstrated an association of AKI when piperacillin-tazobactam was combined with vancomycin, larger and more robust studies are warranted before definitive recommendations can be made on the minimization of piperacillin-tazobactam and vancomycin combination therapy. Until then, antimicrobial stewardship programs should consider utilizing strategies to limit the duration of piperacillin-tazobactam and vancomycin combination therapy in an attempt to decrease the future incidence of AKI.

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