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Nephrotoxicity during Vancomycin Therapy in Combination with Piperacillin-Tazobactam or Cefepime

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ABSTRACT Recent reports have demonstrated that vancomycin (VAN) may lead to an increase in the incidence of acute kidney injury (AKI) when it is combined with antipseudomonal beta-lactams. This study compared the incidence of AKI associated with VAN plus piperacillin-tazobactam (TZP) or cefepime (FEP). This was a retrospective, matched cohort study that was conducted at an academic medical center between September 2010 and September 2014 and that included adult patients without severe chronic or structural kidney disease, dialysis, pregnancy, cystic fibrosis, or a hospital transfer receiving TZP-VAN or FEP-VAN for at least 48 h. The primary outcome was the difference in the AKI incidence between the TZP-VAN and FEP-VAN groups, evaluated using the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria. Patients in the two groups were matched on the basis of age, sex, severity of illness, baseline creatinine clearance, hypotension, number of nephrotoxicity risk factors, and intravenous contrast exposure. In total, 4,193 patients met all inclusion criteria (3,605 received TZP-VAN and 588 received FEP-VAN). The unadjusted AKI incidence was 21.4% in patients receiving TZP-VAN, whereas it was 12.6% in patients receiving FEP-VAN ($P < 0.001$). After the patients were matched, 1,633 patients receiving TZP-VAN and 578 patients receiving FEP-VAN were evaluated. The AKI incidence remained higher in patients receiving TZP-VAN than in those receiving FEP-VAN (21.4% versus 12.5%, $P < 0.0001$). This trend remained true for all classifications of the RIFLE criteria. After controlling for remaining confounders, TZP-VAN therapy was associated with 2.18 times the odds of AKI than FEP-VAN therapy (95% confidence interval, 1.64 to 2.94 times) in logistic regression. AKI was significantly more common in patients receiving vancomycin in combination with piperacillin-tazobactam than in those receiving vancomycin in combination with cefepime. This finding reinforces the need for the judicious use of combination empirical antimicrobial therapy.

KEYWORDS nephrotoxicity, piperacillin-tazobactam, adverse drug effects, beta-lactams, cefepime, vancomycin

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Nephrotoxicity is a well-established adverse effect of vancomycin (VAN) therapy. Risk factors for increased acute kidney injury (AKI) with vancomycin therapy include concomitant administration with nephrotoxic agents, prolonged treatment durations of greater than 7 days, daily vancomycin doses of 4 g or greater, and obesity (1). The incidence of AKI with vancomycin therapy varies widely and is estimated to range from 1.0 to 42% (2–4) Additionally, current guidelines for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections advocate the use of more aggressive dosing to combat the increasing MICs associated with treatment failure (5).

The addition of an antipseudomonal beta-lactam agent, such as piperacillin-tazobactam (TZP) or cefepime (FEP), is common in hospitalized patients. Beta-lactam

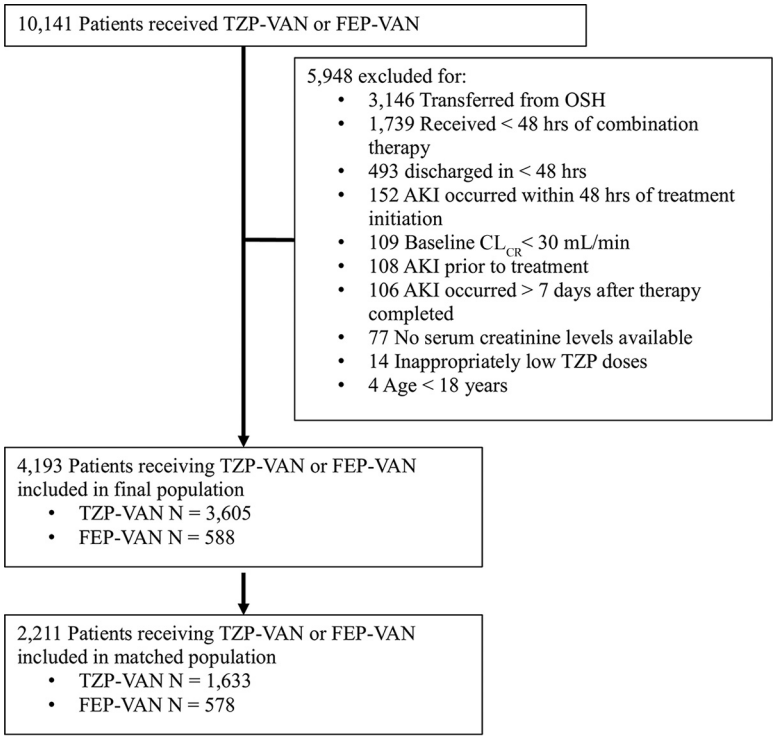

FIG 1 Patient selection diagram. CL_{CR}, creatinine clearance; FEP, cefepime; OSH, outside hospital; TZP, piperacillin-tazobactam; VAN, vancomycin.

antibiotics, primarily penicillin agents and early cephalosporins, have been associated with acute interstitial nephritis (AIN) (6). Cases of cefepime-associated AIN have only recently been reported (7). Recent literature suggests that the combination of VAN and TZP is more nephrotoxic than VAN monotherapy and VAN combined with FEP (8–10). However, the impact of TZP and VAN therapy may not be consistent among all patient populations (11). No clear mechanism for the increase in AKI incidence in combination therapy is known. The rate of AKI associated with TZP-VAN therapy in previous studies ranged from 9.5% to 34.8% in a variety of patient populations (8–16).

The objective of this study was to evaluate the incidence of AKI with two commonly prescribed antibiotic regimens in hospitalized patients, piperacillin-tazobactam with vancomycin and cefepime with vancomycin.

RESULTS

Records for 10,141 patients were screened. After the exclusion criteria were applied (Fig. 1), 4,193 patients were analyzed for all outcomes. Of 3,605 patients receiving TZP-VAN who were evaluated in the unmatched analysis, 1,633 patients were matched to 578 of 588 patients in the FEP-VAN group (>98% of patients were matched). Of the 152 patients excluded due to an AKI occurring within 48 h after treatment initiation, 133 were from the TZP-VAN group (3.6% of the population treated with TZP-VAN) and 19 were from the FEP-VAN group (3.1% of the population treated with FEP-VAN). This difference was not statistically significant ($P = 0.68$), suggesting that the assumption that AKIs occurring prior to 48 h of treatment are independent of drug selection is correct.

At the baseline, the TZP-VAN group was older (51.5 ± 16.0 versus 49.4 ± 17.0 years, $P = 0.006$) and more likely to be male (60.4% versus 55.4%, $P = 0.03$). The severity of illness was similar between the two groups, while patients in the FEP-VAN group had higher baseline creatinine clearance (CL_{CR}) values than patients in the TZP-VAN group (101 ml/min [interquartile range {IQR}, 77 to 133 ml/min] versus 97 ml/min [IQR, 74 to 125 ml/min], $P = 0.01$). Significant differences in nephrotoxic exposures existed be-

TABLE 1 Patient demographic and clinical characteristics[a]

Characteristic	Unmatched cohort			Matched cohort		
	TZP-VAN (n = 3,605)	FEP-VAN (n = 588)	P value	TZP-VAN (n = 1,633)	FEP-VAN (n = 578)	P value
Mean ± SD age (yr)	51.5 ± 16.0	49.4 ± 17.0	0.006	49.7 ± 15.7	49.4 ± 17	0.7
No. (%) of male patients	2,177 (60.4)	326 (55.4)	0.03	905 (55.4)	323 (55.9)	0.9
Median (IQR) CCI	3 (1–6)	3 (1–5)	0.2	3 (1–5)	3 (1–5)	1
Median (IQR) baseline CL_{CR} (ml/min)	97 (74–125)	101 (77–132)	0.01	100 (77–126)	101 (77–132)	0.4
No. (%) of patients with:						
Hypotension	946 (26.2)	190 (32.3)	0.002	479 (29.3)	186 (32.2)	0.2
Dehydration	220 (6.1)	36 (6.1)	1	98 (6.0)	34 (5.9)	1
Nephrotoxic drug exposure	2,190 (60.7)	349 (59.4)	0.5	939 (57.5)	340 (58.8)	0.6
ACEI/ARB	841 (23.3)	139 (23.6)	0.9	370 (22.7)	135 (23.4)	0.8
No. (%) of patients treated with or exposed to:						
Acyclovir	70 (1.9)	33 (5.6)	<0.0001	28 (1.7)	29 (5.0)	<0.0001
An aminoglycoside	473 (13.1)	101 (17.2)	0.01	209 (12.8)	98 (17.0)	0.02
Amphotericin B	63 (1.7)	16 (2.7)	0.1	27 (1.7)	15 (2.6)	0.2
A calcineurin inhibitor	114 (3.2)	19 (3.2)	1	35 (2.1)	19 (3.3)	0.2
Contrast dye	1,632 (45.3)	343 (58.3)	<0.0001	921 (56.4)	336 (58.1)	0.5
Foscarnet	9 (0.2)	1 (0.2)	1	3 (0.2)	1 (0.2)	1
A loop diuretic	1,121 (31.1)	166 (28.2)	0.2	496 (30.4)	160 (27.7)	0.2
An NSAID	547 (15.2)	88 (15.0)	0.9	242 (14.8)	83 (14.4)	0.8
Sulfonamide	66 (1.8)	9 (1.5)	0.7	27 (1.7)	9 (1.6)	1
Tenofovir	21 (0.6)	4 (0.7)	0.8	8 (0.5)	4 (0.7)	0.5
No. (%) of patients with the following no. of risk factors:			0.0003			0.3
0	1,132 (31.4)	177 (30.1)		531 (32.5)	177 (30.6)	
1	1,163 (32.3)	190 (32.3)		528 (32.3)	187 (32.4)	
2	795 (22.1)	113 (19.2)		335 (20.5)	113 (19.6)	
3	379 (10.5)	62 (10.5)		160 (10.4)	60 (10.4)	
≥4	136 (3.8)	46 (7.8)		79 (7.1)	41 (7.1)	
Median (IQR) VAN dose (mg/day)	2,000 (1,500–2,500)	2,083 (1,600–2,737)	<0.0001	2,000 (1,500–2,500)	2,083 (1,600–2,700)	0.002
No. (%) of patients with a daily VAN dose of ≥4,000 mg	39 (1.1)	16 (2.7)	0.002	18 (1.1)	16 (2.8)	0.009
No. (%) of patients with the following maximum VAN trough concn (μg/ml):			0.3			0.7
<10	438 (20.8)	77 (21.1)		213 (21.8)	76 (21.1)	
10–15	507 (24.1)	100 (27.4)		231 (23.7)	98 (27.2)	
15–20	521 (24.8)	88 (24.1)		239 (24.9)	87 (24.2)	
>20	639 (30.4)	100 (27.4)		293 (30.0)	99 (27.5)	
No. of days of antibiotic therapy[c]						
Total	5 (4–8)	5 (4–8)	0.05	5 (4–8)	5 (4–8)	0.4
Combination therapy	3 (3–5)	4 (3–6)	0.001	4 (3–5)	4 (3–6)	0.008
FEP or TZP therapy	5 (3–7)	5 (3–7)	0.8	5 (3–7)	5 (3–7)	0.2
VAN therapy	4 (3–6)	4 (3–7)	<0.0001	4 (3–6)	4 (3–7)	<0.0001

[a]ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; CL_{CR}, creatinine clearance; FEP, cefepime; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; TZP, piperacillin-tazobactam; VAN, vancomycin.

tween the two groups (Table 1). The median number of nephrotoxic risk factors in each group was 1 (IQR, 0 to 2, $P = 0.2$); however, the FEP-VAN group had more patients with ≥4 risk factors (7.8% versus 3.8% in the TZP-VAN group, $P = 0.0003$). Exposure to contrast dye was more frequent in the FEP-VAN group (58.3% versus 45.3% in the TZP-VAN group, $P < 0.0001$). Among patients who had VAN concentrations obtained, no significant difference in VAN exposure was found. However, the FEP-VAN group had statistically higher average daily VAN doses than the TZP-VAN group. The numbers of days of antibiotic therapy were similar between the two groups; however, due to the large sample size and statistical power, the P values are reported to be significant.

TABLE 2 Incidence of AKI in unmatched and matched cohorts[a]

Outcome	Unmatched cohort			Matched cohort		
	No. (%) of patients			No. (%) of patients		
	VAN-TZP (n = 3,605)	VAN-FEP (n = 588)	P value	VAN-TZP (n = 1,633)	VAN-FEP (n = 578)	P value
Any AKI	771 (21.4)	74 (12.6)	<0.0001	349 (21.4)	72 (12.5)	<0.0001
Risk	422 (11.7)	44 (7.5)	0.003	179 (11.0)	42 (7.3)	0.01
Injury	244 (6.8)	21 (3.6)	0.004	113 (6.9)	21 (3.6)	0.006
Failure	105 (2.9)	9 (1.5)	0.08	57 (3.5)	9 (1.6)	0.03

[a]FEP, cefepime; TZP, piperacillin-tazobactam; VAN, vancomycin.

AKI incidence was significantly higher in patients receiving TZP-VAN than in patients receiving FEP-VAN (21.4% versus 12.6%, $P < 0.0001$). Classifications of risk (11.7% for the VAN-TZP group versus 7.5% for the VAN-FEP group, $P = 0.003$) and injury (6.8% for the VAN-TZP group versus 3.6% for the VAN-FEP group, $P = 0.004$) were more common in the TZP-VAN group than the VAN-FEP group. The failure classification was not significantly different between the two groups (Table 2).

Following matching, baseline covariates were well balanced, with the remaining imbalances being present in acyclovir exposure, aminoglycoside exposure, and average daily VAN dose (Table 1). AKI remained more common in the TZP-VAN group (21.4% for the TZP-VAN group versus 12.5% for the VAN-FEP group, $P < 0.0001$), with all levels of the risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria being more common in the TZP-VAN group than the FEP-VAN group (Table 2). FEP-VAN treatment was associated with an average treatment effect of a 10.1% (95% confidence interval [CI], 7.8 to 12.2%) reduction in AKI incidence compared to that for the TZP-VAN group.

After controlling for additional confounders present after matching in the multivariate regression analysis (Table 3), TZP-VAN was associated with 2.18 times the odds of AKI compared to that for FEP-VAN (95% CI, 1.64 to 2.94 times). Other independent risk factors for AKI included dehydration and exposure to acyclovir, amphotericin B, or loop diuretics. VAN doses of between 3 and 4 g daily were associated with an increase in the incidence of AKI (adjusted odds ratio, 1.61; 95% CI, 1.11 to 2.32) compared to that for VAN doses of 1,000 and 1,500 mg per day. A duration of VAN treatment of at least 7 days was associated with 1.47 times the odds of AKI (95% CI, 1.14 to 1.89 times) compared to that associated with VAN treatment for less than 7 days. No evidence of

TABLE 3 Multivariate regression results in matched cohort[a]

Covariate and treatment group	Adjusted odds ratio	CI	P value
TZP-VAN	Reference	Reference	Reference
FEP-VAN	2.18	1.64–2.94	<0.001
VAN dose (mg/day)			
<1,000	0.53	0.16–1.39	0.3
1,000–1,499	1.01	0.72–1.42	0.9
1,500–1,999	Reference	Reference	Reference
2,000–2,499	1.08	0.79–1.48	0.6
2,500–2,999	1.16	0.81–1.65	0.4
3,000–3,999	1.61	1.11–2.32	0.01
≥4,000	1.3	0.5–3.05	0.6
Duration of VAN therapy of ≥7 days	1.47	1.14–1.89	0.003
Acyclovir exposure	2.22	1.17–4.07	0.01
Amphotericin B exposure	2.25	1.14–4.41	0.02
Loop diuretic exposure	2.78	2.22–3.50	<0.001
Calcineurin inhibitor exposure	1.62	0.85–2.98	0.1
Dehydration exposure	1.81	1.18–2.72	0.005

[a]FEP, cefepime; TZP, piperacillin-tazobactam; VAN, vancomycin.

TABLE 4 Secondary endpoints[a]

Characteristic	Unmatched cohort			Matched cohort		
	VAN-TZP (n = 3,605)	VAN-FEP (n = 588)	P value	VAN-TZP (n = 1,633)	VAN-FEP (n = 578)	P value
Median (IQR) time (days) to AKI	5 (3–9)	8 (4–16.8)	0.0006	5 (3–9)	8 (4–17)	0.0004
Median (IQR) hospital length of stay (days)	8 (4–15)	8 (4–17)	0.08	8 (4–15)	8 (5–17)	0.9
No. (%) of patients with in-hospital mortality	276 (7.7)	53 (9.0)	0.3	113 (6.9)	53 (9.2)	0.09

[a]FEP, cefepime; IQR, interquartile range; TZP, piperacillin-tazobactam; VAN, vancomycin.

overfitting was found (Hosmer-Lemeshow P value = 0.53), and the model was adequately predictive with a c-statistic of 0.7.

The results of analyses of secondary objectives are summarized in Table 4. There were no significant differences in the length of stay or mortality. AKI occurred earlier in TZP-VAN-treated patients in both cohorts. The most common TZP dosing regimen in the TZP-VAN group was 3.375 g every 6 h (55.6%), with 4.5 g every 6 h being the second most common regimen (30.4%). AKI incidence was significantly higher in patients receiving TZP at 4.5 g every 6 h than in patients receiving TZP at 3.375 g every 6 h (24.3% versus 20.1%, P = 0.008) but was significant for risk only when stratified on the basis of the RIFLE criteria. The most common FEP regimen was 2 g every 8 h (64.8%), with 2 g every 12 h being the second most common regimen (23.8%). There was no difference in the incidence of AKI between patients receiving the highest FEP dosing regimen and patients receiving all other dosing regimens (13.4% versus 11.1%, P = 0.5).

DISCUSSION

In this retrospective review of a large cohort of patients receiving VAN-TZP or VAN-FEP, we found that the incidence of AKI was significantly higher in patients receiving VAN and TZP concomitantly. To our knowledge, this is the largest study to date to examine the difference in AKI incidence among patients treated with VAN and FEP or PTZ. We found the AKI rate in patients treated with VAN-TZP to be 21.4%, whereas the range of the incidence found in the current literature is 9.5 to 34.8% (8–16). The AKI incidence in the VAN-FEP group was similar to previous reports of 12.5% (9, 10). Of note, the AKI incidence in the VAN-FEP group in our study was significantly lower than that in the study of Hammond et al. (11) (12.5 versus 28.8%), likely due to the dissimilar patient populations evaluated.

In a 2014 review of 139 diabetic patients with osteomyelitis, VAN-TZP was associated with a 29.3% incidence of acute renal failure (defined as an increase in the serum creatinine concentration of 0.5 mg/dl or a 50% increase in the serum creatinine concentration from that at the baseline), whereas the incidence was 13.3% in the VAN-FEP group (P = 0.099) (9). Gomes and colleagues (2014) conducted a retrospective review of 224 patients receiving the combination of VAN and TZP or FEP (10). In univariate analysis, VAN-TZP was associated with an AKI incidence of 34.8%, whereas the incidence was 12.5% for VAN-FEP (P < 0.0001). Additionally, they found that TZP was an independent predictor of AKI in multiple logistic regression modeling. Finally, in a review of 122 critically ill patients, Hammond et al. found no difference in AKI incidence among patients treated with VAN-TZP and VAN-FEP (32.7 versus 28.8%, P = 0.647) (11).

Small sample sizes and a lack of statistical power severely limit the application of the findings from the previous studies. In addition, aside from the study of Gomes et al. (10), confounding was not adequately addressed in the studies, further limiting their application. Our study attempted to rectify these issues by including a larger number of patients (4,193 in the present study versus 485 in the previous studies combined) (9–11) and utilizing a propensity score matching algorithm to control for confounders. The difference in AKI incidence was maintained after controlling for confounders, suggesting that the use of TZP is associated with increasing rates of AKI compared to those achieved with the use of FEP when the drugs are combined with VAN.

The level of vancomycin exposure was statistically significantly different in both the unmatched and matched cohorts; however, the difference between the median daily vancomycin doses is likely clinically irrelevant. To control for the statistical imbalance in the results for doses of greater than 4,000 mg per day, we included vancomycin dose in the multivariate regression analysis and found that vancomycin dose is largely uncorrelated with AKI incidence, with the exception of doses of between 3,000 and 3,999 mg per day. Additionally, we found that a duration of vancomycin therapy of greater than 7 days was associated with higher rates of AKI, independent of treatment group. This may be related to the overall vancomycin exposure and warrants further study. However, when an interaction term between vancomycin dose and a duration of therapy of greater than 7 days was included in the multivariate logistic regression model, no significant interaction was found. Vancomycin trough concentrations were analyzed, but no significant difference between groups was found and no association with AKI was found. This may be because trough concentrations were not obtained for many patients; however, there were no significant differences in the number of patients for whom trough concentrations were obtained between the TZP-VAN and FEP-VAN groups in both the unmatched and matched cohorts.

Among our secondary outcomes, there was a numerically higher rate of in-hospital mortality among patients in the FEP-VAN group, but this did not reach statistical significance. This finding warrants further study; however, FEP-VAN-treated patients had numerically higher rates of hypotension, which may indicate higher rates of acute illness not captured by surrogate variables and a predisposition for the patients to experience mortality.

We found several factors, aside from treatment group, that were independently associated with AKI incidence. This emphasizes that kidney injury is multifactorial. Additionally, the use of other nephrotoxic agents, such as loop diuretics in patients with uncontrolled heart failure, may indicate underlying conditions not captured through our data analysis that may increase the risk of AKI independently of antibiotic selection.

This study has several limitations which must be addressed. Primarily, due to the retrospective nature of this analysis, the demonstration of causality is difficult. However, several mechanisms to make the investigation more rigorous were applied, such as propensity score matching. In addition, rather than using parameter estimates from matched cohorts, counterfactual simulations were utilized to predict the average treatment effect on AKI incidence between groups. We employed a rigorous study design that controlled for major confounders of AKI, such as concomitant nephrotoxic exposure, hypotension, and previous renal disease. The nephrotoxic potential of the agents was assumed to be equal, but this is not necessarily true. Additionally, the binary representation of nephrotoxic exposure does not describe the amount of the agent received; as such, our estimations of the odds of AKI may be artificially elevated. Finally, data were collected retrospectively from the electronic medical record and are subject to inaccuracies documented in that record; however, any bias introduced should be nondifferential.

In conclusion, in this large retrospective study, we found that the AKI incidence among patients who were treated with a combination of piperacillin-tazobactam and vancomycin was significantly higher than that among patients who were treated with cefepime and vancomycin. This finding remained after propensity score matching and after controlling for remaining imbalances in covariates. A mechanism for the increase in AKI incidence among patients treated with piperacillin-tazobactam compared to that among patients treated with cefepime has not been proposed. Further animal and human studies are warranted to elucidate this mechanism.

MATERIALS AND METHODS

Study design and setting. This was a single-center, retrospective matched cohort study of patients admitted to the University of Kentucky HealthCare Medical Center (UKMC) between 1 September 2010 and 1 September 2014. This study was reviewed and approved by the University of Kentucky Institutional Review Board.

Patients received either the combination TZP-VAN or the combination FEP-VAN. VAN was dosed according to institutional policy (17). Serum VAN concentrations were monitored by pharmacists, and dosage adjustments were made as clinically appropriate.

Data source. Patient data were collected from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust (EDT). EDT contains clinical data from the inpatient population of UKMC from 2006 to the present. The data stored in EDT include demographics, financial classification (Medicare, Medicaid, private insurance), provider-level detail (service line), medical diagnosis (International Classification of Diseases 9 [ICD-9] codes), medical procedures (Current Procedural Terminology [CPT] codes), lab tests and results, medication administration details, visit details (age, length of stay, etc.), and vital signs.

Patient selection. Patients were included if they were 18 years of age or older, hospitalized at UKMC between 1 September 2010 and 1 September 2014, and received either of the studied combinations for a minimum of 48 h in which therapy with the antibiotics in the combination overlapped for at least 48 h. Patients were excluded if they had a history of chronic kidney disease (stage 3 or higher, via ICD-9 code) or structural kidney disease, required dialysis, had experienced AKI prior to antibiotic administration, experienced AKI within 48 h of therapy initiation or more than 7 days after the last dose of antibiotics, or had underlying renal dysfunction (defined as an initial creatinine clearance of $\leq$30 ml/min) at the time of antibiotic initiation. Patients were also excluded from the study if they were pregnant, were diagnosed with cystic fibrosis, or were transferred from another hospital. Patients were followed throughout their stay until the time of discharge.

Data collection. Data collected for each patient included demographic data, visit details (length of stay, admitting and primary diagnosis codes), the severity of underlying illness as defined by the Charlson comorbidity index (CCI) (18), all serum creatinine levels determined per visit, receipt of other nephrotoxic agents (listed in Table 1), and any receipt of intravenous contrast agents. The initial serum creatinine concentration was used as the patient's baseline. Hypotension was defined as a diagnosis of hypotension by ICD-9 coding, a mean arterial pressure of less than 60 mm Hg, or the use of vasopressor or inotrope therapy to maintain adequate perfusion. Contrast exposure was defined as exposure to an imaging procedure in which contrast is indicated via Healthcare Common Procedure Coding System (HCPCS) codes. The doses and dosing schedules of the studied antibiotics and all vancomycin serum concentrations were obtained. The number of days of antibiotic therapy was defined as receipt of at least one dose of antibiotic per day.

Study outcomes. The primary outcome was the difference in AKI incidence between the group receiving TZP-VAN and the group receiving FEP-VAN. Secondary outcomes were AKI incidence on the basis of dosing schemes and duration of therapy, the time to AKI from the time of initiation of therapy, hospital length of stay, and mortality (defined as in-hospital mortality or transfer to a hospice facility).

Development of AKI was evaluated using risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE) criteria (19). The RIFLE criteria consist of three severity classes (risk, injury, failure) and two outcomes classes (loss of kidney function, end-stage kidney disease). Risk was defined as a decrease in the glomerular filtration rate (GFR) of at least 25%, injury was defined as a decrease in the GFR of at least 50%, and failure was defined as a decrease in the GFR of 75% or more. The outcomes classes require a diagnosis based on the duration of renal dysfunction and were not evaluated in this study. GFR was estimated with the adjusted Cockcroft-Gault equation (20).

Patient matching. Antibiotic indications were unknown, and antibiotic choice was prescriber specific; therefore, propensity scores for each patient were estimated to control for potential bias. Patients in the TZP-VAN group were matched three to one with patients in the FEP-VAN group using a nearest-neighbor propensity score algorithm (21) without replacement and a caliper of 0.2 on the basis of the following factors: age, gender, CCI, hypotension exposure, risk factor group (defined by the number of nephrotoxic exposures, i.e., 0, 1, 2, 3, and $\geq$4), baseline creatinine clearance, and receipt of intravenous (i.v.) contrast dye. Additionally, patients were matched exactly on the basis of gender, hypotension exposure, risk factor group, and i.v. contrast dye administration.

Statistical analysis. Characteristics between groups were described using basic descriptive statistics, with continuous variables being compared by Student's *t* test or the Wilcoxon rank-sum test and categorical variables being compared by the chi-square test or Fisher's exact test, as appropriate. The average treatment effect was calculated by taking the average difference in the incidence of AKI in 1,000 counterfactual simulations after fitting of logistic regression models based on each treatment group to the opposite population (22, 23). Following propensity score matching, simple logistic regression was performed on all variables. In addition to the remaining covariate imbalances in the matched cohort, the variables with significant associations with AKI in univariate regressions were incorporated into the multivariate logistic regression. All statistical analyses were completed with the RStudio (v0.98) program running R (v3.1.2) software (R Foundation for Statistical Computing, Vienna, Austria) (24, 25). The model fit was assessed by use of the standardized Hosmer-Lemeshow test (26) and the c-statistic. All tests were two-tailed, and significance was defined at an alpha value of 0.05.

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ERRATUM

Erratum for Rutter et al., Nephrotoxicity during Vancomycin Therapy in Combination with Piperacillin-Tazobactam or Cefepime

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Volume 61, no. 2, e02089-16, 2017, https://doi.org/10.1128/AAC.02089-16. Page 4: in Table 3, the first two cells in the "Covariate and treatment group" column were switched. Table 3 should appear as shown below.

TABLE 3 Multivariate regression results in matched cohort[a]

Covariate and treatment group	Odds ratio	CI	*P* value
FEP-VAN	Reference	Reference	Reference
TZP-VAN	2.18	1.64–2.94	<0.001
VAN dose (mg/day)			
<1,000	0.53	0.16–1.39	0.3
1,000–1,499	1.01	0.72–1.42	0.9
1,500–1,999	Reference	Reference	Reference
2,000–2,499	1.08	0.79–1.48	0.6
2,500–2,999	1.16	0.81–1.65	0.4
3,000–3,999	1.61	1.11–2.32	0.01
≥4,000	1.3	0.5–3.05	0.6
Duration of VAN therapy of ≥7 days	1.47	1.14–1.89	0.003
Acyclovir exposure	2.22	1.17–4.07	0.01
Amphotericin B exposure	2.25	1.14–4.41	0.02
Loop diuretic exposure	2.78	2.22–3.50	<0.001
Calcineurin inhibitor exposure	1.62	0.85–2.98	0.1
Dehydration exposure	1.81	1.18–2.72	0.005

[a]FEP, cefepime; TZP, piperacillin-tazobactam; VAN, vancomycin.

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