Acute Kidney Injury in Patients Treated with Vancomycin and Piperacillin-Tazobactam: A Retrospective Cohort Analysis

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BACKGROUND: Empiric antimicrobial therapy often consists of the combination of gram-positive coverage with vancomycin (VAN) and gram-negative coverage, specifically an antipseudomonal beta-lactam such as piperacillin-tazobactam (PTZ). Nephrotoxicity is commonly associated with VAN therapy; however, recent reports show higher nephrotoxicity rates among patients treated with the combination of VAN and PTZ.

OBJECTIVE: This study evaluated the effect of the VAN/PTZ combination on acute kidney injury (AKI) compared to VAN and PTZ monotherapies.

DESIGN, SETTING, AND PATIENTS: This is a retrospective cohort analysis of adult patients without renal disease receiving VAN, PTZ, or the combination from September 1, 2010 through August 31, 2014 at an academic medical center.

MEASUREMENTS: The primary outcome was AKI incidence as defined by the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria.

METHODS: Continuous and categorical variables were assessed with appropriate tests. Univariate and multivariate logistic regressions were performed to assess for associations between variables and AKI incidence. Subanalyses based on severity of illness were performed.

RESULTS: Overall, 11,650 patients were analyzed, with 1647 (14.1%) developing AKI. AKI was significantly more frequent in the VAN/PTZ group (21%) compared to either monotherapy group (VAN 8.3%, PTZ 7.8%, $P < 0.001$ for both). Combination therapy was independently associated with higher AKI odds compared to monotherapy with either agent (adjusted odds ratio [aOR], 2.03; 95% confidence interval [CI], 1.74-2.39; aOR, 2.31; 95% CI, 1.97-2.71, for VAN and PTZ, respectively). Receipt of concomitant nephrotoxic drugs was independently associated with increased AKI rates, as were increased duration of therapy, hospital length of stay, increasing severity of illness, and increasing baseline renal function.

CONCLUSIONS: In this study of more than 10,000 patients, VAN combined with PTZ was associated with twice the odds of AKI development compared to either agent as monotherapy. This demonstrates the need for judicious use of combination empiric therapy. *Journal of Hospital Medicine* 2017;12:77-82. © 2017 Society of Hospital Medicine

Empiric antimicrobial therapy often consists of the combination of gram-positive coverage with vancomycin (VAN) and gram-negative coverage, specifically an antipseudomonal beta-lactam such as piperacillin-tazobactam (PTZ). Literature from a variety of patient populations reports nephrotoxicity associated with VAN, targeting troughs greater than 15 µg/mL, that occur in 5% to 43% of patients.[1] In a study of critically ill patients, acute kidney injury (AKI) was found in 21% of patients receiving VAN, with increasing duration of VAN treatment, greater VAN levels, concomitant vasoactive medication administration, and intermittent infusion methods being associated with higher odds of AKI.[2] A recent report from adult internal medicine patients estimated the incidence of VAN-associated nephrotoxicity at 13.6% and implicated concomitant PTZ therapy as a key factor in these patients.[3]

Further studies have explored the interaction between empiric beta-lactam and VAN therapy, showing mixed results. Reports of AKI associated with the combination of VAN and PTZ range from 16.3% to 34.8%,[4-8] while the cefepime-VAN combination is reported to range from 12.5% to 13.3%.[5,6] While VAN monotherapy groups were well represented, only 1 study[7] compared the PTZ-VAN combination to a control group of PTZ monotherapy.

The primary objective of this study was to evaluate the differences in AKI incidence between patients treated with VAN and with PTZ, alone and in combination.

METHODS

This is a retrospective cohort study of adult patients conducted at the University of Kentucky Chandler Medical Center (UKMC) from September 1, 2010 through August 31, 2014. Patients were included if they were at least 18 years of age on admission; remained hospitalized for at least 48 hours; received VAN combined with PTZ (VAN/PTZ), VAN alone, or PTZ alone; and had at least 48 hours of therapy (and 48 hours of overlapping therapy in the VAN/PTZ group). Patients were excluded if they had underlying diagnosis of chronic kidney disease according to the International Classification of Diseases 9 (ICD-9) code, were re-

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ceiving renal replacement therapy before admission, had a diagnosis of cystic fibrosis, or were pregnant. Additionally, patients were excluded if they presented with AKI, defined as an initial creatinine clearance less than 30 mL/min, or if baseline creatinine clearance was greater than 4 times the standard deviation from the mean; serum creatinine values were not obtained during admission; and if AKI occurred prior to therapy initiation, within 48 hours of initiation, or more than 7 days after treatment was discontinued. Patients were followed throughout their stay until time of discharge.

Data Source

Patient data were collected from the University of Kentucky Center for Clinical and Translational Science Enterprise Data Trust (EDT). The EDT contains clinical data from the inpatient population of UKMC from 2006 to present. Data stored and updated nightly by the EDT includes: demographics, financial classification (Medicare, Medicaid, private insurance), provider-level detail (service line), medical diagnosis (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. This study was approved by the UKMC Institutional Review Board.

Data collected for each patient included: demographic data, visit details (length of stay, admitting and primary diagnosis codes, etc.), severity of underlying illness as defined by the Charlson Comorbidity Index (CCI), all serum creatinine levels drawn per visit, medication administration information (dose, date, and time administered), all VAN trough levels, receipt of other nephrotoxic agents, blood pressures, and receipt of vasopressors.

Outcome Ascertainment

The definition of AKI was based on the RIFLE (Risk, Injury, Failure, Loss, End-stage) criteria,[9] with risk defined as a 25% to 50% decrease in estimated glomerular filtration rate (GFR), injury as a 50% to 75% decrease in estimated GFR, and failure defined as a greater than 75% decrease in estimated GFR. Loss and end-stage classifications were not assessed because of this study's follow-up period. The adjusted Cockcroft and Gault equation[10] was used to estimate GFR due to the inconsistency of weight availability in the dataset and concordance with the institution's practice. Baseline creatinine clearance was calculated with the first serum creatinine obtained, and the minimum creatinine clearance was calculated using the maximum serum creatinine during each patient's visit. The percent decrease in creatinine clearance was calculated from these 2 values. AKI status was defined as meeting any of the RIFLE criteria. Mortality was assessed for all patients and defined as the composite of inhospital mortality and discharge or transfer to hospice care.

Exposure Ascertainment

Hypotension exposure was defined as experiencing 1 of the following: mean arterial blood pressure less than 60 mm Hg, a diagnosis of hypotension by a physician, or receipt of vasopressors or inotropic agents. Days of therapy for each drug were obtained and combination days of therapy were calculated by including only those days in which the patient received both medications. Total days of therapy were calculated by the sum of all days receiving at least 1 study agent. Exposure to other nephrotoxic agents (eg, acyclovir, angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists, aminoglycosides, amphotericin B, cyclosporine, foscarnet, loop diuretics, nonsteroidal anti-inflammatory drugs, sulfonamides, tacrolimus, and tenofovir) were defined as receipt of at least 1 dose of the agent during hospitalization.

Statistical Analysis

Characteristics between groups were described with basic descriptive statistics. Continuous variables were compared with 1-way analysis of variance (ANOVA) or the Kruskal-Wallis test. Categorical variables were compared with chi-square or Fisher exact test. Yearly AKI trends were assessed with Pearson correlation coefficient. To control for differences in underlying severity of illness between groups, a subanalysis was performed in which the cohort was split into 4 groups (0, 1, 2 to 4, and ≥5 points) based on CCI. Univariate models for all covariates were created with probability of AKI as the outcome. Covariates significant after univariate were incorporated into the multivariate model, which was subsequently adjusted to achieve the highest predictive accuracy by minimizing the Akaike information criterion (AIC). Nephrotoxic agent exposures were included in the final multivariate model regardless of statistical significance in univariate analysis. Model fit was assessed with a standardized Hosmer-Lemeshow goodness-of-fit test.[11] All statistical analyses were completed with RStudio v 0.98 running R v 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).[12] All tests were 2-tailed and significance was defined at an alpha of 0.05.

RESULTS

Of 17,879 patients initially screened, 11,650 patients were evaluated, of which 5,497 received VAN and PTZ (VAN/PTZ), 3,055 received VAN alone, and 3,098 received PTZ alone. Table 1 contains basic demographic information. The mean age of patients was 52.5 years ± 16.8 years with 6,242 (53.6%) males. Patients receiving VAN/PTZ had higher CCIs than either monotherapy group and had significantly increased length of hospitalization. While patients in the combination therapy group were more likely to experience hypotension, concomitant nephrotoxic agent exposure was more common in the VAN monotherapy group.

RIFLE-defined AKI occurred in 1,647 (14.1%) across the entire cohort. AKI occurred in 21% of VAN/PTZ patients, 8.3% of VAN patients, and 7.8% of PTZ patients ($P < 0.0001$). RIFLE-defined risk, injury, and failure occurred more frequently in the VAN/PTZ cohort compared to the VAN and PTZ monotherapy groups (Figure). There were no

TABLE 1. Baseline Characteristics

Outcome	VAN	PTZ	VAN/PTZ	*P* value
	(n = 3055)	(n = 3098)	(n = 5497)	
Age (y) [mean (± SD)]	52.5 (16.9)	53.3 (17.5)	52.0 (16.3)	0.003
Age group (y)				<0.0001
18-29	333 (10.9%)	379 (12.2%)	594 (10.8%)	
30-49	940 (30.8%)	837 (27.0%)	1736 (31.6%)	
50-64	984 (32.2%)	1034 (33.4%)	1904 (34.6%)	
65-79	630 (20.6%)	632 (20.4%)	1019 (18.5%)	
≥80	168 (5.5%)	216 (7.0%)	244 (4.4%)	
Male gender	1462 (47.9%)	1523 (49.2%)	3257 (59.3%)	<0.0001
CCI [median (IQR)]	2 (0-4)	2 (0-5)	3 (1-5)	<0.0001
Baseline creatinine clearance (mL/min) [mean (±SD)]	100.9 (40.4)	100.1 (42.7)	101.9 (43.6)	0.2
CrCl group (mL/min)				<0.0001
30-59	394 (12.9%)	528 (17.0%)	855 (15.6%)	
60-89	984 (32.2%)	888 (28.7%)	1539 (28.0%)	
≥90	1677 (54.9%)	1682 (54.3%)	3103 (56.4%)	
Transfer from outside facility	646 (21.1%)	867 (28.0%)	1487 (27.1%)	<0.0001
Admission type				<0.0001
Elective	904 (29.6%)	398 (12.8%)	644 (11.7%)	
Emergency	1329 (43.5%)	1692 (54.6%)	2956 (53.8%)	
Trauma	102 (3.3%)	137 (4.4%)	524 (9.5%)	
Urgent	720 (23.6%)	871 (28.1%)	1373 (25.0%)	
Hypotension exposure	447 (14.6%)	442 (14.3%)	1560 (28.4%)	<0.0001
Dehydration diagnosis	98 (3.2%)	225 (7.3%)	312 (5.7%)	<0.0001
Length of stay (d) [median (IQR)]	5 (3-9)	5 (3-9)	7 (4-14)	<0.0001
Length of stay (d)				<0.0001
≤7	2084 (68.2%)	2144 (69.2%)	2760 (50.2%)	
8-14	596 (19.5%)	641 (20.7%)	1438 (26.2%)	
15-21	182 (6.0%)	179 (5.8%)	637 (11.6%)	
>21	193 (6.3%)	134 (4.3%)	662 (12.0%)	
Nephrotoxic agent exposure	1970 (64.5%)	1434 (46.3%)	3343 (60.8%)	<0.0001
Acyclovir	202 (6.6%)	19 (0.6%)	109 (2.0%)	<0.0001
ACE inhibitor	595 (19.5%)	545 (17.6%)	1142 (20.8%)	0.002
ARB	159 (5.2%)	133 (4.3%)	167 (3.0%)	<0.0001
Aminoglycoside	336 (11.0%)	126 (4.1%)	630 (11.5%)	<0.0001
Amphotericin B	30 (1.0%)	11 (0.4%)	78 (1.4%)	<0.0001
Contrast	165 (5.4%)	257 (8.3%)	418 (7.6%)	<0.0001
Cyclosporine	8 (0.3%)	12 (0.4%)	13 (0.2%)	0.4
Foscarnet	4 (0.1%)	1 (0.03%)	5 (0.1%)	0.4
Loop diuretic	594 (19.4%)	607 (19.6%)	1,828 (33.3%)	<0.0001
NSAID	874 (28.6%)	309 (10.0%)	752 (13.7%)	<0.0001
Sulfonamide	19 (0.6%)	18 (0.6%)	95 (1.7%)	<0.0001
Tacrolimus	34 (1.1%)	75 (2.4%)	108 (2.0%)	0.0006
Tenofovir	27 (0.9%)	18 (0.6%)	29 (0.5%)	0.1
Total therapy (d) [median (IQR)]	3 (2-5)	4 (3-6)	5 (4-8)	<0.0001

NOTE: Reported values are n (%) unless otherwise specified. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCI, Charlson Comorbidity Index; CrCl, creatinine clearance; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; PTZ, piperacillin-tazobactam; SD, standard deviation; VAN, vancomycin; VAN/PTZ, vancomycin and piperacillin-tazobactam combination.

differences in AKI rates between years studied ($r^2 = 0.4732$, $P = 0.2$). Patients in the VAN/PTZ group experienced AKI on average of 8.0 days after treatment initiation, compared to 8.7 days and 5.2 days for VAN and PTZ monotherapy groups, respectively. The composite of inhospital mortality and transfer-to-hospice care was more common in VAN/PTZ patients (9.6%) compared to monotherapy groups (VAN, 3.9%; PTZ, 3.4%), most likely due to the increased severity of illness.

In the subgroup analysis of patients with similar CCI, AKI

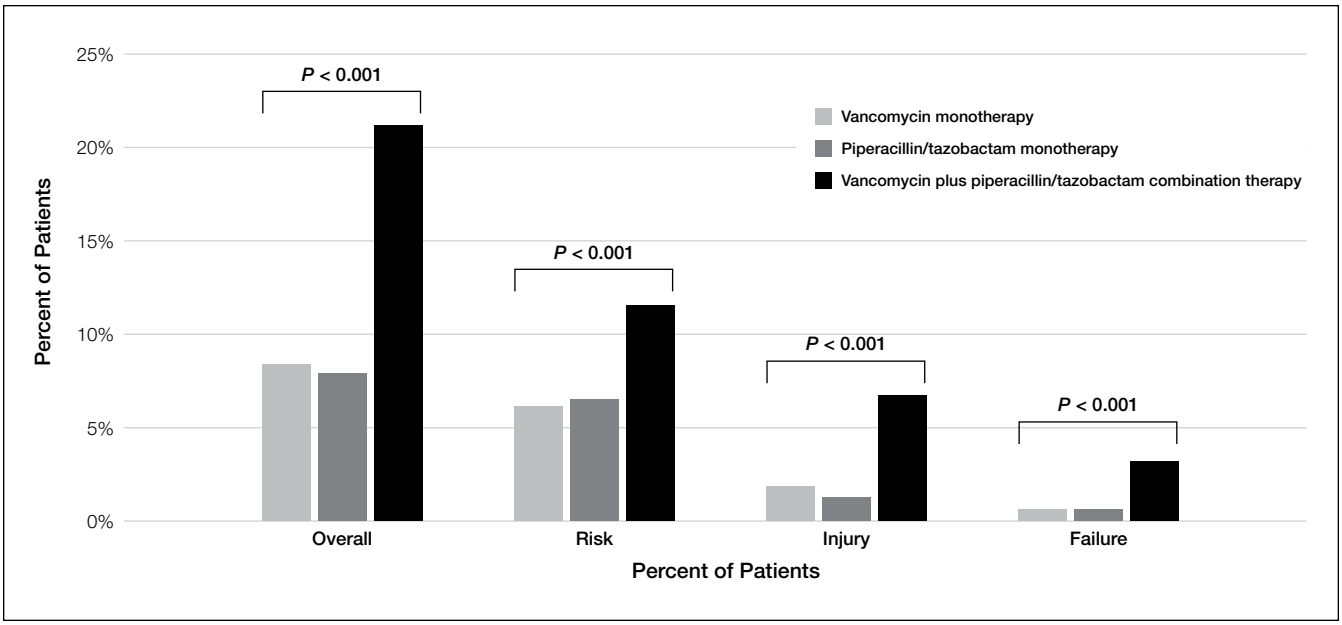

FIG. Unadjusted incidence of acute kidney injury.

incidence increased with severity of illness. When CCI was 0, 7.5% of patients experienced AKI compared to 11.2%, 16.4%, and 18.9% of patients when CCI was 1, 2 to 4, and ≥5, respectively ($P < 0.0001$). VAN/PTZ (range = 12.1% to 26.5%) was associated with greater AKI incidence than either VAN (range = 4.8% to 11.5%) or PTZ (range = 3.8% to 10.4%) alone in each subgroup ($P < 0.0001$ for all subgroups).

Factors associated with AKI in univariate analyses included treatment with VAN/PTZ, days of therapy, baseline creatinine clearance, transfer from outside hospitals, CCI, admission type, length of hospitalization, dehydration exposure, and hypotension exposure. Exposure to aminoglycosides, amphotericin B, ACE inhibitors, nonsteroidal anti-inflammatory drugs, tacrolimus, foscarnet, loop diuretics, sulfonamides, and tenofovir were all associated with increased odds of AKI in simple univariate logistic regression. Gender, age, year of treatment, angiotensin II receptor antagonist exposure, and cyclosporine exposure were not significantly associated with AKI incidence.

After multivariate logistic regression, monotherapy with VAN or PTZ was associated with decreased odds of AKI compared to VAN/PTZ therapy (aOR_{VAN}, 0.48; 95% CI_{VAN}, 0.41-0.57; aOR_{PTZ}, 0.43; 95% CI_{PTZ}, 0.37-0.50). No difference in AKI incidence was observed between VAN and PTZ groups ($aOR_{PTZ:VAN}$, 0.88; 95% CI, 0.73-1.08). Table 2 describes the relationship between AKI and other covariates included in the model. Increased odds of AKI were seen with concomitant administration of ACE inhibitors, amphotericin B, tacrolimus, loop diuretics, and tenofovir. Radio-contrast dye administration was associated with lower odds of AKI. Patients admitted urgently and emergently were at higher risk of AKI, while those admitted via the trauma center were less likely to experience AKI compared to patients who were electively admitted. Increased length of stay and duration of therapy were both associated with increased likelihood of AKI, independent of treatment group; however, durations of therapy beyond 12 days was not associated with increased AKI. Hypotension, as defined, and diagnosed dehydration both independently increased AKI odds. Aside from those older than 80 years of age, increasing age was not associated with increased AKI risk. Male gender was associated with a slight decrease in AKI rate. No evidence of overfitting was observed with the standardized Hosmer-Lemeshow *P*-value of 0.683, and the model provides good predictive accuracy with a C-statistic of 0.788.

CONCLUSIONS

Acute kidney injury secondary to VAN therapy is a well-characterized adverse effect, while AKI incidence secondary to PTZ is less understood. Additionally, there appears to be an additive effect when these agents are used in combination. This is the largest review of AKI in patients receiving VAN,PTZ, or the combination of both agents.

There is increasing evidence suggesting greater nephrotoxicity in patients treated with the combination of VAN and antipseudomonal beta-lactams. The mechanism for the apparent increase in nephrotoxicity with this drug combination is not well understood and needs further study in both animal models and humans.

Acute kidney injury rates related to VAN vary widely, with recent studies in critically ill and internal medicine patients estimated at 21% and 13.6%, respectively.[2,3] In our VAN monotherapy cohort, the AKI rate was 8.3%, with 2.3% of patients experiencing a greater than 50% decrease in creatinine clearance. Piperacillin-tazobactam-related AKI rates are not well characterized; however, a small retrospective analysis estimated that 11.1% of PTZ patients experienced acute renal failure (defined as either increase

TABLE 2. Univariate and Multivariate Association between Combination VAN/PTZ Therapy and AKI Odds Independent of Other Baseline Covariates

Covariate	Unadjusted			Adjusted		
	OR	95% CI	*P*	aOR	95% CI	*P*
Treatment group						
PTZ/VAN		(referent)			(referent)	
VAN	0.34	0.29-0.39	**<0.001**	0.48	0.41-0.57	**<0.0001**
PTZ	0.32	0.27-0.37	**<0.001**	0.43	0.37-0.5	**<0.0001**
Male gender	0.99	0.89-1.10	0.896	0.85	0.75-0.95	**0.0049**
Age (y)						
18-29		(referent)			(referent)	
30-49	1.09	0.91-1.32	0.361	0.99	0.8-1.22	0.908
50-64	1.23	1.02-1.48	**0.031**	1.06	0.85-1.31	0.618
64-79	1.11	0.91-1.36	0.316	1.17	0.92-1.5	0.209
≥80	1.12	0.84-1.47	0.427	1.77	1.26-2.48	**0.0009**
CCI (per point)	1.07	1.06-1.09	**<0.001**	1.04	1.02-1.06	**<0.0001**
Baseline CrCl (mL/min)						
30 to <60		(referent)			(referent)	
60 to <90	1.02	0.85-1.23	0.816	1.41	1.15-1.74	**0.0012**
≥90	1.7	1.45-2.01	**<0.001**	3.39	2.76-4.16	**<0.0001**
Admission type						
Elective		(referent)			(referent)	
Emergency	1.19	1.02-1.39	**0.033**	1.22	1.02-1.45	**0.033**
Trauma	1.03	0.79-1.33	0.82	0.5	0.37-0.66	**<0.0001**
Urgent	1.63	1.38-1.94	**<0.001**	1.39	1.13-1.7	**0.0016**
Transfer from outside facility	1.56	1.39-1.74	**<0.001**	1.16	1-1.33	**0.044**
Hypotension exposure	2.81	2.52-3.15	**<0.001**	1.6	1.4-1.83	**<0.0001**
Dehydration exposure	1.29	1.04-1.59	**0.018**	1.31	1.04-1.66	**0.0246**
Nephrotoxic drug exposures						
Acyclovir	1.22	0.90-1.63	0.182	1.05	0.76-1.47	0.757
ACE inhibitor	1.34	1.18-1.51	**<0.001**	1.15	1-1.33	**0.048**
Aminoglycoside	1.89	1.62-2.20	**<0.001**	1.15	0.96-1.37	0.131
Amphotericin B	4.35	2.99-6.27	**<0.001**	2.25	1.48-3.44	**0.0002**
ARB	0.87	0.65-1.15	0.347	1.17	0.85-1.59	0.335
Contrast dye	1.26	1.04-1.51	**0.017**	0.79	0.64-0.98	**0.0291**
Cyclosporine	1.35	0.50-3.06	0.506	0.74	0.26-2.12	0.571
Foscarnet	6.09	1.69-21.92	**0.004**	2.06	0.44-9.67	0.358
Loop diuretic	3.51	3.15-3.91	**<0.001**	2.02	1.77-2.31	**<0.0001**
NSAIDs	0.82	0.71-0.95	**0.009**	0.98	0.83-1.16	0.809
Sulfonamide	1.8	1.18-2.68	**0.005**	1.39	0.88-2.19	0.156
Tacrolimus	2.66	1.97-3.56	**<0.001**	2.11	1.48-3	**<0.0001**
Tenofovir	1.96	1.12-3.28	**0.013**	1.93	1.06-3.5	**0.0314**
Year of admission						
2010		(referent)				
2011	0.85	0.69-1.05	0.127			
2012	0.95	0.78-1.18	0.657			
2013	0.87	0.70-1.07	0.176			
2014	0.84	0.67-1.05	0.121			
Duration of therapy (d)						
2-3		(referent)			(referent)	
4-5	1.81	1.55-2.13	**<0.001**	1.32	1.11-1.56	**0.0013**
6-7	3.23	2.74-3.81	**<0.001**	1.8	1.5-2.15	**<0.0001**
8-9	5.09	4.22-6.13	**<0.001**	2.02	1.63-2.51	**<0.0001**
10-11	5.94	4.71-7.46	**<0.001**	1.98	1.52-2.58	**<0.0001**
12-13	5.25	3.84-7.12	**<0.001**	1.41	0.99-1.99	0.0543
≥14	5.31	4.19-6.72	**<0.001**	1.28	0.95-1.71	0.103
Length of stay (d)						
<7		(referent)			(referent)	
8-14	3.35	2.94-3.81	**<0.001**	2.05	1.76-2.39	**<0.0001**
15-21	4.48	3.79-5.29	**<0.001**	2.33	1.89-2.87	**<0.0001**
>21	5.88	5.01-6.91	**<0.001**	2.81	2.25-3.51	**<0.0001**

NOTE: Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CCI, Charlson Comorbidity Index; CrCl, creatinine clearance; NSAID, nonsteroidal anti-inflammatory drug; PTZ, piperacillin-tazobactam; VAN, vancomycin; VAN/PTZ, vancomycin plus piperacillin-tazobactam.

in serum creatinine greater than 0.5 mg/dL or 50% increase from baseline).[13] In the present study, we found the PTZ-related AKI rate to be 7.8%, which may be due to a more stringent definition of AKI. Additionally, Hellwig et al[13] found that PTZ monotherapy was associated with higher AKI rates compared to VAN monotherapy (11.1% vs 4.9%; $P = 0.014$). This was not replicated in our study, with VAN and PTZ monotherapy having similar AKI rates (8.3% and 7.8%, respectively) and an adjusted aOR of 0.88 (95% CI 0.0.73-1.08) for AKI in PTZ- compared to VAN-treated patients. The estimated AKI incidence of 21% in the combination therapy group at our institution is consistent with literature that ranges from 16.3% to 34.8%.[4-8, 13]

To control for differences in baseline severity of illness, we performed a subgroup analysis of patients with similar CCI scores. The finding of increased AKI in patients receiving combination VAN and PTZ was consistent in each subgroup, suggesting that the increase in AKI is independent of illness severity.

This study is not without limitations. As with all retrospective studies, it is difficult to determine a causal link between VAN and PTZ combination therapy and increased AKI incidence due to confounding. We employed a rigorous study design that controlled for major confounders of AKI, such as concomitant nephrotoxic exposure, hypotension, and renal disease. Severity of illness was measured with CCI, which may not accurately capture the severity of illness at treatment initiation. Alternatives, such as acute physiology and chronic health evaluation (APACHE) and sequential organ failure assessment (SOFA) scores, may more accurately reflect critical illness on presentation; however, this study was not focused specifically on critically ill patients. In addition to baseline comorbidity, we controlled for hypotension and dehydration as a surrogate marker for critical illness. In the subgroup analysis of patients with similar CCI, the effect of VAN/PTZ on AKI compared to VAN or PTZ monotherapy was consistent in each group. Nephrotoxic potential of agents was assumed to be equal, which 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 AKI odds may be artificially elevated. Approximately one-quarter of the patients in this study were transferred from an outside hospital, for which no data regarding initial treatment are available. This may lead to exposure misclassification. We attempted to control for this factor in the regression model and found that, after controlling for other covariates, hospital transfer was associated with increasing odds of AKI. Finally, data were collected retrospectively from the electronic medical record and are subject to inaccuracies documented in the chart; however, any bias introduced should be nondifferential.

In our large retrospective study of combination empiric therapy with VAN and PTZ, we found that combination therapy was associated with more than double the odds of AKI occurring compared to either monotherapy with VAN or PTZ. Increasing duration of therapy was also associated with increases in AKI. These findings demonstrate the need for judicious use of combination therapy and strengthen the need for antimicrobial de-escalation when appropriate to avoid deleterious effects.

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