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Acute Kidney Injury in Non-Intensive Care and Intensive Care Patients Treated with Vancomycin and Piperacillin-Tazobactam

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Background: We investigated the incidence of acute kidney injury (AKI) and risk factors associated with vancomycin (VAN) and piperacillin-tazobactam (TZP) combination therapy in non-intensive care unit (ICU) and ICU settings.

Methods: In this single-center retrospective cohort study, adults who received VAN for ≥48 h during the period from 1 January 2016 through 31 December 2017 were included. The primary endpoint was incidence of AKI.

Results: Data from 593 adults were analyzed. The incidence of AKI was 10.6% overall, 8.0% in the non-TZP group, and 19.8% in the TZP group. In univariate analysis, the odds ratio (OR) for AKI was higher in the TZP group than in the non-TZP group (2.84, 95% CI = 1.64-4.90). In both the non-ICU and ICU settings, the OR for AKI was higher in the TZP group than in the non-TZP group (non-ICU: OR = 3.04, 95% CI = 1.52-6.09; ICU: OR = 2.51, 95% CI = 1.03-6.08). Furthermore, in propensity score analysis, the OR for AKI was higher in the TZP group than in the non-TZP group (OR = 2.81, 95% CI = 1.52-5.17). In both the non-ICU and ICU settings, the OR for AKI was higher in the TZP group than in the non-TZP group (non-ICU: OR = 2.57, 95% CI = 1.17-5.64; ICU: OR = 3.51, 95% CI = 1.05-11.6).

Conclusions: Combined use of TZP in patients receiving VAN increased AKI incidence in non-ICU and ICU settings. (J Nippon Med Sch 2020; 87: 66–72)

Key words: acute kidney injury, vancomycin, piperacillin-tazobactam, intensive care unit, nephrotoxicity

Introduction

Hospitalized patients frequently develop acute kidney injury (AKI), which increases morbidity and mortality[1,2]. Vancomycin (VAN) is a glycopeptide antibiotic commonly used in clinical practice for treatment of gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus*. The risk of AKI during VAN treatment is widely known (AKI incidence rate, 5-7%[3,4]). High-dose VAN administration and elevated trough concentrations of VAN during treatment are associated with AKI[5,6].

Recent studies have reported an association between AKI and VAN plus piperacillin-tazobactam (TZP) combination therapy[7–14]. However, studies of AKI risk after VAN and TZP combination therapy were small observational studies and yielded varying results. In addition, it is unclear if any particular combination of drugs is associated with increased AKI risk in an intensive care unit (ICU) setting[9–12].

Therefore, this study investigated AKI incidence and risk factors associated with VAN and TZP combination therapy in non-ICU and ICU settings. We categorized patients who developed AKI as non-ICU and ICU patients and assessed whether AKI caused by VAN plus TZP was related to AKI severity.

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Materials and Methods

Study Design and Setting

This single-center, retrospective cohort study was conducted at Nippon Medical School Hospital, a tertiary academic hospital in Tokyo, Japan. This study was reviewed and approved by the Institutional Review Board of Nippon Medical School Hospital before data collection (30-05-937).

Study Sample

Adult patients who received VAN for ≥48 h during the period from 1 January 2016 through 31 December 2017 at Nippon Medical School were included. Patients were excluded for the following reasons: (1) age <18 years, (2) renal replacement therapy before VAN, and (3) underlying renal dysfunction (defined as serum creatinine concentration >1.5 mg/dL or calculated creatinine clearance <30 mL/min, based on the Cockcroft-Gault equation).

Data Collection

The following data were captured from electronic medical records: age, sex, comorbidities (hypertension, diabetes mellitus, myocardial infarction, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease, liver disease, human immunodeficiency virus infection, malignant solid tumor, and hematological malignancy), infection site, ICU status at onset of VAN therapy, serum creatinine concentrations, VAN serum trough concentrations, concurrent administration of TZP for ≥48 h, concomitant administration of nephrotoxins (cyclosporine, tacrolimus, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, tenofovir, loop diuretics, sulfamethoxazole trimethoprim, amphotericin B, aminoglycoside, foscarnet, iodine agents, acyclovir, methotrexate, and cisplatin), and dates and doses of targeted medications administered (VAN, TZP, and concomitant nephrotoxins). The initial load administered was defined as a dose ≥1.5 times that of the second and subsequent doses at the time of initial VAN administration.

To assess the effect of VAN serum trough concentrations on AKI development, mean trough VAN concentrations before AKI development were calculated. For patients who developed AKI, only trough values obtained before AKI onset were used.

Study Endpoints

The primary endpoint was incidence of AKI. Determination of AKI was based on the RIFLE criteria (risk, injury, failure, loss, and end-stage; increase in creatinine level to twice that of baseline or a 50% decrease in calculated creatinine clearance)[15] or renal replacement therapy introduction after VAN for the following indications: (1) refractory hyperkalemia, (2) refractory acidemia and metabolic acidosis, (3) refractory pulmonary edema due to fluid overload, or (4) symptoms or complications attributable to uremia[16]. The secondary endpoint was in-hospital mortality.

Statistical Analysis

All statistical analyses were performed with SPSS software, v.25 (IBM, Armonk, NY, USA). A sample size of 540 patients (180 ICU patients and 360 non-ICU patients) was estimated to be required, assuming a 10% incidence of nephrotoxicity in patients receiving VAN and an 80% power to detect a minimal increase of 20% in nephrotoxicity for patients in the non-TZP group, as compared with patients in the TZP group, using the two-sided chi-square test at a significance (α) level of 0.05. Potential associations between AKI and in-hospital mortality were evaluated with the chi-square test or Fisher exact test.

In addition, we used propensity score analysis with inverse probability of treatment weighting (IPTW) to adjust for treatment selection bias (with or without TZP)[17]. On the basis of clinical knowledge, possible confounders were selected for their potential association with TZP treatment. The predicted probability was calculated by fitting a logistic regression model that included all clinically relevant variables, as shown in **Table 1**. After weighting by propensity score, the odds ratios (OR) of AKI were analyzed by using the generalized estimating equations method[18]. Predictors of AKI were selected in accordance with previous studies[5,6]. Standardized differences were used to assess the balance of confounders between treatment with or without TZP, as described by Austin[19]. A standardized difference of <0.1 suggested a negligible difference in the mean or prevalence of covariates between treatments.

Results

A total of 924 patients were screened. Of these, 331 were excluded: 16 because of age (<18 years), 174 for receiving renal replacement therapy, and 141 because of underlying renal dysfunction. A total of 593 patients were thus included, 462 of whom received antibiotic therapy without TZP (non-TZP group) and 131 received antibiotic therapy with TZP (TZP group; **Figure 1**). Baseline patient characteristics are shown in **Table 1**. Overall, 31.5% patients were treated in an ICU setting, and the most common indication for antibiotics was bacteremia (36.3%). Treatment characteristics are shown in **Table 2**. A total of 68.6% pa-

Table 1 Baseline patient characteristics

Characteristics	all (n=593) non-TZP (n=462)		TZP (n=131)		non-ICU setting (n=406) non-TZP (n=319)		TZP (n=87)		ICU setting (n=187) non-TZP (n=143)		TZP (n=44)	
	n (%) [Mean, SD]				n (%) [Mean, SD]				n (%) [Mean, SD]			
Age	[64.8, 16.2]		[64.4, 16.5]		[66.2, 15.1]		[63.9, 16.5]		[62.1, 14.2]		[66.7, 15.4]		[65.4, 15.6]		[71.0, 14.4]	
Female	197	(33.2%)	155	(33.5%)	42	(32.1%)	148	(36.5%)	119	(37.3%)	29	(33.3%)	49	(26.2%)	36	(25.2%)	13	(29.5%)
TZP use	131	(22.1%)					87	(21.4%)					44	(23.5%)				
Comorbidities																		
HT	179	(30.2%)	138	(29.9%)	41	(31.3%)	85	(20.9%)	68	(21.3%)	17	(19.5%)	94	(50.3%)	70	(49.0%)	24	(54.5%)
CI	69	(11.6%)	50	(10.8%)	19	(14.5%)	24	(5.9%)	15	(4.7%)	9	(10.3%)	45	(24.1%)	35	(24.5%)	10	(22.7%)
Liver disease	78	(13.2%)	55	(11.9%)	23	(17.6%)	60	(14.8%)	42	(13.2%)	18	(20.7%)	18	(9.6%)	13	(9.1%)	5	(11.4%)
Solid tumor	99	(16.7%)	84	(18.2%)	15	(11.5%)	73	(18.0%)	66	(20.7%)	7	(8.0%)	26	(13.9%)	18	(12.6%)	8	(18.2%)
Infection site																		
Pneumonia	124	(20.9%)	92	(19.9%)	32	(24.4%)	66	(16.3%)	47	(14.7%)	19	(21.8%)	58	(31.0%)	45	(31.5%)	13	(29.5%)
Bacteremia	215	(36.3%)	165	(35.7%)	50	(38.2%)	119	(29.3%)	97	(30.4%)	22	(25.3%)	96	(51.3%)	68	(47.6%)	28	(63.6%)
Skin/soft tissue	65	(11.0%)	51	(11.0%)	14	(10.7%)	45	(11.1%)	35	(11.0%)	10	(11.5%)	20	(10.7%)	16	(11.2%)	4	(9.1%)
Intra-abdominal	55	(9.3%)	46	(10.0%)	9	(6.9%)	35	(8.6%)	29	(9.1%)	6	(6.9%)	20	(10.7%)	17	(11.9%)	3	(6.8%)
Serum creatinine (mg/dL)	[0.74, 0.27]		[0.74, 0.27]		[0.74, 0.27]		[0.73, 0.26]		[0.73, 0.26]		[0.71, 0.24]		[0.75, 0.30]		[0.75, 0.30]		[0.74, 0.31]	

SD, standard deviation; HT, hypertension; CI, cerebrovascular disease.

tients received nephrotoxic agents. Mean overall duration of VAN therapy was 12.8 days. Mean overall VAN trough concentration was 13.4 ± 4.8 μg/mL. In 93.6% of patients, VAN trough concentration was appropriately maintained at below 20 μg/mL[5,6].

AKI incidence was 10.6% overall (63 of 593 patients), 8.0% in the non-TZP group (37 of 462 patients), and 19.8% in the TZP group (26 of 131 patients). In univariate analysis, the OR for AKI was higher in the TZP group than in the non-TZP group (OR = 2.84, 95% CI = 1.64-4.90). In the non-ICU setting, AKI incidence was 6.9% in the non-TZP group (22 of 319 patients) and 18.4% in the TZP group (16 of 87 patients). In the ICU setting, AKI incidence was 10.5% in the non-TZP group (15 of 143 patients) and 22.5% in the TZP group (10 of 44 patients). In both the non-ICU and ICU settings, the OR for AKI was higher in the TZP group than in the non-TZP group (non-ICU: OR = 3.04, 95% CI = 1.52-6.09; ICU: OR = 2.51, 95% CI = 1.03-6.08; **Table 3**). In univariate analysis excluding patients with a mean VAN trough concentration >20 μg/mL, the OR for AKI was higher in the TZP group than in the non-TZP group (OR = 2.77, 95% CI = 1.48-5.18).

In-hospital mortality was 9.8% overall (58 of 593 patients), 8.9% in the non-TZP group (41 of 406 patients), and 13.0% in the TZP group (17 of 187 patients, p = 0.16).

All 593 patients were included in propensity score analysis with IPTW. The balance of confounders between treatment groups after weighting was satisfactory. In multivariable analysis after weighting, the OR for AKI was higher in the TZP group than in the non-TZP group (OR = 2.81, 95% CI = 1.52-5.17). In both the non-ICU and ICU settings, the OR for AKI was higher in the TZP group than in the non-TZP group (non-ICU: OR = 2.57, 95% CI = 1.17-5.64; ICU: OR = 3.51, 95% CI = 1.05-11.6). Long-term VAN therapy (>14 days) and high VAN serum trough concentration (mean trough concentration > 20 μg/mL) were also associated with AKI. There was no other statistically significant association with AKI in propensity score analysis (**Table 4**).

Discussion

Combined use of VAN and TZP increased AKI incidence by a factor of two to three in non-ICU and ICU settings. The results of multivariate analysis using propensity scores were consistent and indicated that combined use of TZP and VAN increased AKI, regardless of severity.

VAN plus TZP is the most widely used antibiotic com-

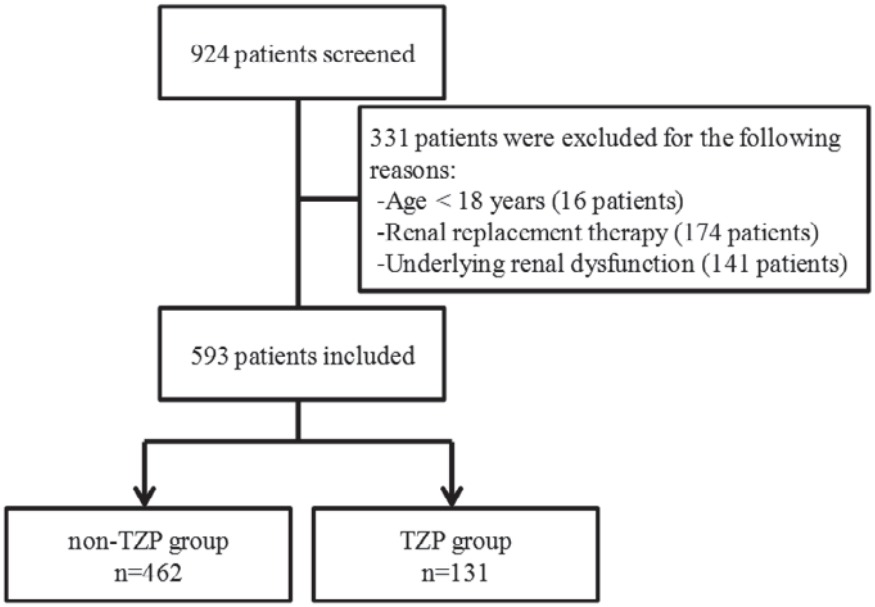

Fig. 1 Patient selection process
A total of 924 patients were screened. Of these, 331 patients were excluded: 16 because of age (<18 years), 174 for receiving renal replacement therapy, and 141 because of underlying renal dysfunction. A total of 593 patients were included: 462 received antibiotic therapy without TZP (non-TZP group), and 131 received antibiotic therapy with TZP (TZP group).

bination therapy in hospitals[20]. Several recent observational studies have reported increased risk of AKI with VAN plus TZP combination therapy. Early studies reported an AKI incidence of 18% to 49%[13,14]. More recently, Navilkele et al. compared a patient group receiving VAN plus TZP with one receiving VAN plus cefepime. AKI incidence was 29% in the VAN plus TZP group and 11% in the VAN plus cefepime group, although the detection power for ICU patients was insufficient[8]. A systematic review and meta-analysis of the association between AKI and VAN plus TZP combination therapy[21] identified 15 published studies and 17 conference abstracts, including at least 34,799 patients, and reported an incidence rate of AKI of 16.7% overall, 22.2% in a VAN plus TZP group, and 12.9% in a non-TZP control group, although data for critically ill patients were limited. In our study, the overall OR was 2.81, which is similar to previously reported values.

Buckley et al. reported no association between AKI incidence and VAN plus TZP or VAN plus cefepime combination treatment in ICU settings, which is inconsistent with our results[12]. They suggested that introduction of renal replacement therapy after antibiotic therapy treatment should not be regarded as AKI, which might explain the discrepancy between past and present results. Furthermore, there were differences between centers in indications for renal replacement therapy in ICU settings[16,22,23]. According to Buckley et al., 10% of patients in the VAN plus TZP group received renal replacement therapy; however, in our study, only 4.5% of patients in the VAN plus TZP group in ICU received renal replacement therapy. Introduction of renal replacement therapy may have influenced AKI incidence. Early introduction of renal replacement therapy may have decreased incidence of AKI associated with VAN and TZP in ICU. Future studies should attempt to clarify the risk of AKI attributable to combined use of VAN and TZP in critically ill patients, including randomized controlled trials to establish indications for renal replacement therapy.

The mechanism underlying the association of AKI with VAN plus TZP combination therapy is not well understood. Our findings suggest that the increase in AKI incidence caused by TZP administration is independent of VAN blood concentration, although there is also a mechanism independent of VAN blood concentration. Future studies should investigate the mechanism of AKI development.

This is the first study with adequate statistical power to investigate the association of AKI risk with VAN and TZP combination therapy in non-ICU and ICU settings. Patients who developed AKI were classified by setting as non-ICU and ICU patients, and the incidence of AKI due

Table 2 Treatment characteristics

	all (n=593)						non-ICU setting (n=406)						ICU setting (n=187)					
	non-TZP (n=462)				TZP (n=131)		non-TZP (n=319)				TZP (n=87)		non-TZP (n=143)				TZP (n=44)	
Characteristics	n (%) [Mean, SD]						n (%) [Mean, SD]						n (%) [Mean, SD]					
Nephrotoxic agents																		
CyA	23	(3.9%)	14	(3.0%)	9	(6.9%)	22	(5.4%)	14	(4.4%)	8	(9.2%)	1	(0.5%)	0	(0.0%)	1	(2.3%)
Tac	17	(2.9%)	13	(2.8%)	4	(3.1%)	15	(3.7%)	12	(3.8%)	3	(3.4%)	2	(1.1%)	1	(0.7%)	1	(2.3%)
NSAIDs	83	(14.0%)	68	(14.7%)	15	(11.5%)	53	(13.1%)	44	(13.8%)	9	(10.3%)	30	(16.0%)	24	(16.8%)	6	(13.6%)
ACEI	38	(6.4%)	29	(6.3%)	9	(6.9%)	15	(3.7%)	10	(3.1%)	5	(5.7%)	23	(12.3%)	19	(13.3%)	4	(9.1%)
ARB	64	(10.8%)	48	(10.4%)	16	(12.2%)	37	(9.1%)	27	(8.5%)	10	(11.5%)	27	(14.4%)	21	(14.7%)	6	(13.6%)
Tenofovir	4	(0.7%)	2	(0.4%)	2	(1.5%)	4	(1.0%)	2	(0.6%)	2	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Loop diuretics	177	(29.8%)	123	(26.6%)	54	(41.2%)	112	(27.6%)	76	(23.8%)	36	(41.4%)	65	(34.8%)	47	(32.9%)	18	(40.9%)
SMX/TMP	67	(11.3%)	55	(11.9%)	12	(9.2%)	59	(14.5%)	49	(15.4%)	10	(11.5%)	8	(4.3%)	6	(4.2%)	2	(4.5%)
AmB	31	(5.2%)	18	(3.9%)	13	(9.9%)	23	(5.7%)	12	(3.8%)	11	(12.6%)	8	(4.3%)	6	(4.2%)	2	(4.5%)
Aminoglycoside	9	(1.5%)	7	(1.5%)	2	(1.5%)	4	(1.0%)	3	(0.9%)	1	(1.1%)	5	(2.7%)	4	(2.8%)	1	(2.3%)
Foscarnet	3	(0.5%)	3	(0.6%)	0	(0.0%)	2	(0.5%)	2	(0.6%)	0	(0.0%)	1	(0.5%)	1	(0.7%)	0	(0.0%)
Iodine agents	126	(21.2%)	103	(22.3%)	23	(17.6%)	62	(15.3%)	52	(16.3%)	10	(11.5%)	64	(34.2%)	51	(35.7%)	13	(29.5%)
ACV	65	(11.0%)	44	(9.5%)	21	(16.0%)	58	(14.3%)	40	(12.5%)	18	(20.7%)	7	(3.7%)	4	(2.8%)	3	(6.8%)
MTX	29	(4.9%)	23	(5.0%)	6	(4.6%)	29	(7.1%)	23	(7.2%)	6	(6.9%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
CDDP	5	(0.8%)	3	(0.6%)	2	(1.5%)	5	(1.2%)	3	(0.9%)	2	(2.3%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Any use of the above agents	407	(68.6%)	313	(67.7%)	94	(71.8%)	273	(67.2%)	210	(65.8%)	63	(72.4%)	134	(71.7%)	103	(72.0%)	31	(70.5%)
Duration of VAN (days)	[12.8, 12.7]		[11.9, 11.7]		[15.9, 15.3]		[14.0, 13.4]		[13.0, 12.6]		[17.3, 15.3]		[10.0, 10.3]		[9.3, 8.7]		[12.4, 14.2]	
Mean of VAN trough (μg/mL)	[13.4, 4.8]		[13.1, 5.0]		[14.3, 3.9]		[13.4, 4.5]		[13.0, 4.6]		[14.6, 3.6]		[13.5, 5.5]		[13.4, 5.8]		[13.8, 4.4]	
Mean of VAN trough>20 μg/mL	38	(6.4%)	29	(6.2%)	9	(6.8%)	22	(5.4%)	16	(5.0%)	6	(6.8%)	16	(8.5%)	13	(9.0%)	3	(6.8%)
Fluid volume (mL)	[1,928.7, 1,242.5]		[1,875.3, 1,231.1]		[2,116.7, 2,045.9]		[1,472.5, 915.6]		[1,427.2, 913.7]		[1,640.3, 948.8]		[2,924.7, 1,281.7]		[2,882.0, 1,259.5]		[3,062.4, 1,356.8]	
VAN loading dose	129	(21.8%)	101	(21.9%)	28	(21.4%)	75	(18.5%)	62	(19.4%)	13	(14.9%)	54	(28.9%)	39	(27.3%)	15	(34.1%)

SD, standard deviation; CyA, cyclosporine; NSAIDs, non-steroidal anti-inflammatory drugs; ACEI, angiotensin converting-enzyme inhibitors;
ARB, angiotensin II receptor blockers; SMX/TMP, sulfamethoxazole trimethoprim; AmB, amphotericin B; ACV, acyclovir; MTX, methotrexate; CDDP, cisplatin.
Fluid volume, amount of 24hours fluid administration after initial VAN use.

Table 3 Univariable association between piperacillin-tazobactam (TZP) use and acute kidney injury (AKI)

	AKI incidence (n, (%))					
		non-TZP	TZP	OR	[95% CI]	p
all	63/593 (10.6%)	37/462 (8.0%)	26/131 (19.8%)	2.84	[1.64-4.90]	0.0003
non-ICU	38/406 (9.3%)	22/319 (6.9%)	16/87 (18.4%)	3.04	[1.52-6.09]	0.003
ICU	25/187 (13.3%)	15/143 (10.5%)	10/44 (22.5%)	2.51	[1.03-6.08]	0.045

OR, odds ratio; CI, confidence interval.

Table 4 Multivariate analysis for acute kidney injury (AKI) with inverse probability of treatment weighting to adjust for treatment selection bias

	all			non-ICU			ICU		
	OR	[95% CI]	p	OR	[95% CI]	p	OR	[95% CI]	p
TZP use	2.81	[1.52-5.17]	0.001	2.57	[1.17-5.64]	0.018	3.51	[1.05-11.6]	0.041
VAN>14 days	2.37	[1.16-4.83]	0.017	2.80	[1.00-7.80]	0.049	5.00	[1.49-16.7]	0.009
Nephrotoxic agents	1.67	[0.74-3.73]	0.214	2.57	[1.07-6.14]	0.033	0.84	[0.21-3.22]	0.8
Fluid volume>2,000 mL	0.95	[0.47-1.87]	0.873	0.70	[0.21-2.30]	0.555	0.39	[0.07-2.13]	0.389
Loading dose of VAN	1.32	[0.61-2.81]	0.476	0.83	[0.24-2.86]	0.771	1.96	[0.66-5.81]	0.225
VAN trough>20 μg/mL	16.33	[6.67-39.9]	<0.001[a]	19.46	[5.01-75.5]	<0.001[b]	20.19	[5.51-73.8]	<0.001[c]

a=9.22E-10; b=1.80E-5; c=6.00E-6

OR, odds ratio; CI, confidence interval.

to VAN plus TZP differed in relation to AKI severity. The results for the non-ICU and ICU patients were similar and suggest that VAN and TZP combination therapy increases AKI risk, regardless of severity. Multivariate analysis using an IPTW method was performed as sensitivity analysis, and the results remained consistent, which indicates that they are robust. AKI onset during hospitalization greatly affects the mortality rate, and avoiding treatment-related AKI is therefore a priority[1,2]. Use of antimicrobials other than VAN and TZP, such as carbapenem, fourth-generation cephalosporin, daptomycin, and linezolid, may improve treatment outcomes for patients with infections.

This study has several limitations. First, it was a retrospective observational study, and the possibility of treatment selection bias thus cannot be excluded. However, propensity score analysis using the IPTW method, to adjust for bias of treatment selection, yielded similar results. Nevertheless, since adjustment for unknown and thus unmeasured confounding factors was not possible, further studies are needed. Second, there was insufficient evidence for an association between severity and AKI incidence. Because severity data were missing for many patients in this study, we could not evaluate severity scores, including sequential organ failure assessment and acute physiology and chronic health evaluation (APACHE) scores. Future studies should attempt to determine whether the risk of AKI associated with VAN and TZP combination therapy correlates with severity. Finally, we did not consider beta-lactam agents other than TZP in our study, as there are no reports of increased AKI risk associated with the use of such agents and VAN.

In conclusion, combined use of TZP in patients receiving VAN increased AKI incidence, and the results were similar in non-ICU and ICU settings. These findings suggest that VAN and TZP combination therapy increases AKI risk, regardless of severity.

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