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Original Article

# Concomitant vancomycin and piperacillin/tazobactam treatment is associated with an increased risk of acute kidney injury in Japanese patients

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ABSTRACT

*Introduction:* Recent studies have corroborated that the co-administration of vancomycin (VCM) and piperacillin/tazobactam (PT) is correlated with an increased incidence of acute kidney injury (AKI). However, evidence directed at the Japanese population is scarce. Therefore, we conducted a retrospective study to compare the occurrence of AKI among Japanese patients who received VCM with PT (VP therapy) and VCM with another β-lactams (VA therapy).

*Methods:* The present study, performed at Tsuyama Chuo Hospital between June 2012 and December 2018, included adult patients who received VCM and β-lactam antibiotics for ≥48 h. We defined the primary outcome as the incidence of AKI based on the risk, injury, failure, loss, and end-stage kidney disease criteria. Patients' clinical characteristics and outcomes were reviewed and compared between the two groups with univariate and multivariate logistic regression analyses. Subgroup analysis was conducted by stratifying the patients' baseline hospital admittance status, as intensive care unit or general wards.

*Results:* We analyzed 272 patients (92 V P therapy and 180 VA therapy). Univariate analysis revealed a significant difference in AKI development between VP and VA therapy (25.0% vs 12.2%; $p < 0.01$). A multivariate analysis demonstrated that VP therapy and VCM initial trough levels ≥15 μg/mL were associated with an incidence of AKI. Patients at general wards, rather than those admitted at an intensive care unit, developed AKI with VP therapy ($p = 0.02$).

*Conclusion:* VP therapy was associated with an increased risk of AKI compared to that with VA therapy among the Japanese population.



## 1. Introduction

Antimicrobials with broad gram-positive and gram-negative activities are necessary for treating patients with severe infection, especially in-hospital settings [1]. Vancomycin (VCM) and piperacillin (PIPC)/tazobactam (PT) are frequently co-administered as an empiric therapy to mainly cover antimicrobial-resistant pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* [1,2]. These antimicrobials are often combined as empirical therapy for patients with severe infections.

Nephrotoxicity is a well-known adverse effect of VCM [3] and β-lactam agents [4]. Recently, several investigators have reported that combination treatment comprising VCM and PT (VP therapy) results in an increased risk of acute kidney injury (AKI) [5–11]. Furthermore, some literature based on systematic reviews and meta-analyses have demonstrated that the occurrence of AKI is significantly associated with patients undergoing VP therapy, compared to those with VCM alone, PT alone, and VCM combined with another β-lactams (VA therapy) [12–15]. However, these previous studies did not include Japanese populations, and the risk of developing AKI in Japanese patients with VP therapy is yet to be uncovered.

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**Abbreviations**

| | |
|---|---|
| AKI | acute kidney injury |
| CFPM | cefepime |
| CIs | confidential intervals |
| CLcr | creatinine clearance |
| DM | diabetes mellitus |
| GW | general ward |
| ICU | intensive care unit |
| IQRs | interquartile ranges |
| MRSA | methicillin-resistant *Staphylococcus aureus* |
| ORs | odds ratios |
| PIPC | piperacillin |
| qSOFA | quick sequential organ failure assessment |
| RIFLE | risk, injury, failure, loss, and end-stage kidney disease |
| SCr | serum creatinine |
| PT | piperacillin/tazobactam |
| TDM | therapeutic drug monitoring |
| VCM | vancomycin |

Drug elimination is roughly divided into two pathways, hepatic metabolism and renal excretion. In general, ethnic differences exist in cytochrome-related hepatic functions [16], whereas the difference in drug renal excretion among distinct racial groups has not been elucidated scientifically. Both VCM and PIPC are excreted outside the human body via the renal excretion system; thus, there seems to be no plausible explanation for the individual risk of VP therapy-associated AKI in Japanese. However, the number of nephrons is reportedly smaller in Japanese individual than in those from Western countries [17], suggesting that the renal function of Japanese individuals could be inherently fragile. This ethnic difference should be further clarified in the future, but investigating the individual risk of VP therapy-induced AKI among Japanese patients is required.

Recently, two studies were conducted to elucidate the relationship between VP therapy and the incidence of AKI in Japanese populations. One indicated that VP therapy might result in AKI with a significantly higher incidence rate compared to that with a combination of VCM and carbapenems (33.3% vs 9.1%) [18]. This study covered only patients administered carbapenems (meropenem and doripenem) as controls and included a small number of subjects (82 patients in total). Another Japanese study included 593 patients, and showed that VP therapy can be associated with an increased risk of AKI incidence compared to that with VCM without PT (19.8% vs 8.0%) [19]. However, in that study, it was unclear which antibiotics were co-administered and whether VCM was given as a monotherapy or not in the VCM without the PT group. We, therefore, conducted this study to assess the incidence of AKI among those receiving VP therapy and VA therapy in Japanese populations.

## 2. Patients and methods

### 2.1. Study design and patients

This retrospective cohort study was conducted at Tsuyama Chuo Hospital, a 515-bed acute-care community hospital in Okayama, Japan, between June 2012 and December 2018. The study protocol was approved by the Ethics Committee of Tsuyama Chuo Hospital (No. 418) with a waiver of informed consent due to the retrospective nature of this research. Adult patients (≥18 years) co-administered intravenous VCM and β-lactam antibiotics for ≥48 h, both of which were started within 24 h of each other, were included in this study. For patients administered VCM and β-lactams multiple times during their treatment courses, only the first therapeutic regimen was included. Patients whose baseline serum creatinine (SCr) was more than 1.2 mg/dL [11] and who required hemodialysis at the onset of combination therapy were excluded. Moreover, patients who were administered VCM with both PT and another β-lactam during VCM therapy were also excluded.

### 2.2. Outcomes and definitions

The primary outcome of this study was the development of AKI, which was defined as an increase in SCr by 1.5-fold or 0.5 mg/dL from baseline by referring to the risk, injury, failure, loss, and end-stage kidney disease (RIFLE) criteria [20]. Patients were stratified into three categories according to SCr elevation as follows: risk with an increase in SCr 1.5-fold; injury with a doubling of SCr; failure with an increase in SCr 3-fold and/or SCr >4 mg/dL. SCr used to determine the presence of AKI was collected until 2 days after the completion of combination therapy. A retrospective medical chart review was performed for data of the patients' clinical characteristics including age, sex, body weight, co-morbidities, intensive care unit (ICU) admission when the combination was initiated, SCr, creatinine clearance (CLcr), intubation, nosocomial infection, overall VCM treatment duration, combination therapy duration, quick sequential organ failure assessment (qSOFA) scores [21], and the presence of sepsis. CLcr was calculated using the Cockcroft-Gault equation [22]. Nosocomial infections were defined as those that occurred >48 h after hospitalization. When patients were evaluated as having a qSOFA score of two or more at baseline, we defined them as septic. The preceding baseline values were based on each patient's chart at the initiation of combination therapy. Concomitant nephrotoxin use was also examined as receiving at least one dose of the following agents during the combination therapy based on the definitions provided by previous studies [11,23,24]: acyclovir, aminoglycosides, amphotericin B, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, calcineurin inhibitors, colistin, ganciclovir, intravenous contrast, loop diuretics, non-steroidal anti-inflammatory agent, and vasopressors. Patients' initial VCM trough levels were evaluated if the patients underwent VCM therapeutic drug monitoring (TDM). Patients were divided into two groups according to the VCM combination (VP therapy or VA therapy) and we compared the clinical characteristics and outcomes between them. *Anti*-pseudomonal β-lactams were defined as those classified as aztreonam, carbapenems, cefepime (CFPM), and ceftazidime. Moreover, we performed a subgroup analysis by stratifying patients' baseline hospital admittance status when starting either VP therapy or VA therapy as ICU or general ward (GW) care.

### 2.3. Statistical analysis

Continuous variables were reported as medians and interquartile ranges (IQRs) and assessed with the Mann-Whitney *U* test. Categorical variables were reported as numbers and percentages and assessed with Fisher's exact tests. Odds ratios (ORs) with their 95% confidential intervals (CIs) were calculated for the categorical variables. Based on the preceding literature [25], development of AKI was also evaluated by multivariate logistic regression analysis, including nine covariates as follows: sex, age, ICU admission when the combination was initiated, sepsis, concomitant nephrotoxin use, diabetes mellitus (DM), VCM treatment duration, VCM initial trough ≥15 μg/mL, and VP therapy. The data were analyzed using EZR software, a graphic user interface for R 3.0.0 software (The R Foundation for Statistical Computing, Vienna, Austria) [26]. All

reported $p$ values less than 0.05 were considered statistically significant.

## 3. Results

During this study period, a total of 272 patients who underwent a combination of VCM and β-lactam therapy were identified, including 92 receiving VP therapy and 180 receiving VA therapy (Fig. 1). The baseline clinical characteristics of the two groups are shown in Table 1. Among the various background parameters, the univariate analysis revealed a significant difference in the comorbidity of DM alone (25.0% vs 11.7%; $p < 0.01$). Among those who underwent VA therapy, 68 cases (37.8%) were co-administered *anti*-pseudomonal β-lactams with VCM. Proportions of each drug co-administered in VA therapy are shown in Table 2. Of all patients, TDM analyses of VCM were performed for 251 patients (92.3%) including 85 V P therapy (92.4%) and 166 VA therapy (92.2%) patients. The median initial VCM trough levels were not significantly different between the two groups (13.3 vs 13.4 μg/mL; $p = 0.67$). The primary outcome, the rate of AKI incidence, was significantly higher in the VP group than in the VA group (25.0% vs 12.2%; $p < 0.01$; OR [95% C.I.], 2.39 [1.18, 4.83]). Focusing on each RIFLE category, although the AKI incidence rates were not significantly different in the Risk and Injury category ($p = 0.27$, 0.14, respectively), they were significantly higher in the Failure category (5.4% vs 1.1%; $p = 0.05$).

The results of multivariate logistic regression analysis for the incidence of AKI are shown in Table 3. Among the nine parameters, the combination of VCM with PT and VCM initial trough levels ≥15 μg/mL were significantly associated with the onset of AKI. In the subgroup analysis (Table 4), there were 74 ICU patients, 23 receiving VP therapy and 51 receiving VA therapy. There was no significant difference between the groups, including the development of AKI. In contrast, there were 198 GW patients, 69 receiving VP therapy and 129 receiving VA therapy. Although the backgrounds of the patients were mostly identical (except for DM), the rate of AKI incidence was significantly higher in the VP therapy patients (26.1% vs 12.4%, $p = 0.02$; OR [95% CI] 2.48 [1.10, 5.67]; Table 4).

## 4. Discussion

In this study, an increased risk of developing AKI was observed when VCM was co-administered with PT rather than with other β-lactams. Our results were similar to those of the previous studies conducted abroad [5,6,8,9,11–15], suggesting that a risk of AKI should also be noted for the Japanese population when combining VCM and PT. Although the incidence of AKI in each RIFLE category was higher in VP patients than in VA patients, a statistically significant difference was observed only in the Failure category (Risk, Injury, and Failure; $p = 0.27$, 0.14, and 0.05, respectively). This may have been due to small sample size and the consequent lack of statistical power. Because they tend to have low numbers of renal nephrons [17], patients in the Japanese population might have inherently fragile renal function; thus, AKI may be more severe in patients from Japan than in patients from Western countries. Compared to a similar study targeting Japanese patients [18], our study included a larger number of patients (272 subjects) who were administered various β-lactams such as penicillins, cephems, and carbapenems. Additionally, compared to another study conducted on Japanese patients [19], our study included more detailed data on antibiotic therapy including which β-lactam was co-administered with VCM. Thus, the present study potentially provides more robust and interpretable data.

Possible explanations for the development of AKI with VP therapy are additive or synergistic nephrotoxicity of the drug combination. First, VCM nephrotoxicity is generally associated with an accumulation of the drug in the proximal renal tubule [27], causing acute tubular necrosis and consequently AKI. Several factors such as older age, longer duration of VCM therapy, concomitant nephrotoxic agents, high VCM trough levels, and a critically-ill state are reported as risk factors for VCM-associated nephrotoxicity [3]. Multivariate analysis showed that a VCM initial trough of ≥15 μg/mL is associated with AKI incidence (OR, 3.19). The Japanese practice guidelines for VCM TDM recommend a VCM trough level of

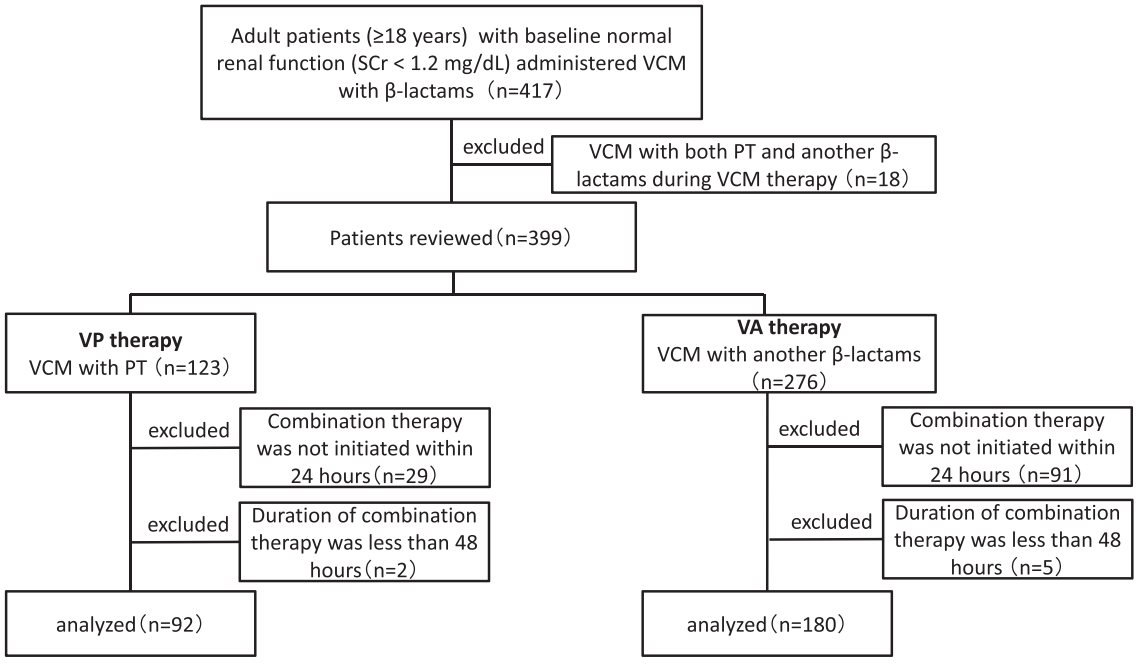


**Fig. 1.** The flow of the present study. VCM, vancomycin; PT, piperacillin/tazobactam; SCr, serum creatinine.

**Table 1**
Univariate analysis for clinical characteristics and outcome of patients treated with VP and VA therapies.

| | VP (N = 92) | VA (N = 180) | *p* value | Odds ratio (95% CI) |
|---|---|---|---|---|
| Male (%) | 57 (62.0) | 109 (60.6) | 0.90 | 1.06 (0.61, 1.84) |
| Age [IQR], year | 77.5 [69.8, 85] | 76.0 [65.8, 83] | 0.14 | – |
| Weight [IQR], kg | 52.5 [44.3, 60.0] | 53 [46.2, 63.3] | 0.34 | – |
| SCr [IQR], mg/dL | 0.69 [0.60, 0.86] | 0.73 [0.60, 0.88] | 0.44 | – |
| CLcr [IQR], mL/min | 58.0 [46.3, 76.7] | 61.7 [50.1, 80.8] | 0.18 | – |
| VCM treatment duration [IQR], days | 7 [4, 14] | 7 [4, 12] | 0.70 | – |
| Combination duration [IQR], days | 6 [4, 9] | 7 [4, 11] | 0.23 | – |
| Concomitant use of nephrotoxins (%) | 63 (68.5) | 122 (67.8) | 1 | 1.03 (0.58, 1.85) |
| ICU admission when initiated the combination (%) | 23 (25.0) | 51 (28.3) | 0.67 | 0.84 (0.45, 1.54) |
| Nosocomial infection (%) | 54 (58.7) | 87 (48.3) | 0.12 | 1.52 (0.89, 2.61) |
| Intubation (%) | 9 (9.8) | 22 (12.2) | 0.69 | 0.78 (0.30, 1.86) |
| qSOFA | | | | |
| 0 (%) | 29 (31.5) | 55 (30.6) | 0.89 | 1.05 (0.58, 1.86) |
| 1 (%) | 35 (38.0) | 69 (38.3) | 1 | 0.99 (0.57, 1.71) |
| 2 (%) | 20 (21.7) | 31 (17.2) | 0.41 | 1.33 (0.67, 2.61) |
| 3 (%) | 8 (8.7) | 25 (13.9) | 0.24 | 0.59 (0.22, 1.43) |
| Sepsis (qSOFA≥2) (%) | 28 (30.4) | 56 (31.1) | 1 | 0.97 (0.54, 1.72) |
| Comorbid conditions (%) | | | | |
| Malignancy | 34 (37.0) | 55 (30.6) | 0.34 | 1.33 (0.76, 2.33) |
| Diabetes mellitus | 23 (25.0) | 21 (11.7) | <0.01 | 2.51 (1.24, 5.13) |
| Chronic heart failure | 6 (6.5) | 11 (6.1) | 1 | 1.07 (0.31, 3.29) |
| COPD | 3 (3.3) | 9 (5.0) | 0.76 | 0.64 (0.11, 2.65) |
| Hepatic cirrhosis | 3 (3.3) | 0 | – | – |
| Chronic renal failure | 0 | 1 (0.6) | – | – |
| TDM analysis for VCM (%) | 85 (92.4%) | 166 (92.2%) | 1 | – |
| VCM initial trough level [IQR], μg/mL | 13.3 [9.8, 20.0] | 13.4 [9.3, 19.3] | 0.57 | – |
| VCM initial trough ≥15 μg/mL (%) | 36 (39.1) | 70 (38.9) | 1 | 1 (0.58, 1.74) |
| Development of AKI (%) | 23 (25.0) | 22 (12.2) | <0.01 | 2.39 (1.18, 4.83) |
| Risk | 11(12.0) | 14 (7.8) | 0.27 | 1.61 (0.63, 4.01) |
| Injury | 7 (7.6) | 6 (3.3) | 0.14 | 2.38 (0.66, 8.86) |
| Failure | 5 (5.4) | 2 (1.1) | 0.05 | 5.08 (0.81, 54.34) |
| Loss | 0 | 0 | – | – |
| ESKD | 0 | 0 | – | – |

VP, vancomycin with piperacillin/tazobactam; VA, vancomycin with another β-lactam; CI, confidential intervals; IQR, interquartile range; SCr, serum creatinine; CLcr, creatinine clearance; VCM, vancomycin; ICU, intensive care unit; qSOFA, quick sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury; ESKD, end-stage kidney disease.
Continuous variables were compared by the Mann-Whitney *U* test and categorical variables were compared by the Fisher's exact tests. Odds ratios were calculated for the categorical variables.

10–20 μg/mL as a preferable range [28] with 10–15 μg/mL initially for safety concerns. When treating serious infections caused by MRSA, however, VCM initial trough concentrations of 15–20 μg/mL are recommended. Our data showed that a higher VCM concentration is significantly associated with AKI development.

Second, PT also possibly induces AKI with relatively high frequency by triggering acute interstitial nephritis [4]. The affinity of PIPC for renal transporters is reportedly high and thus, the concomitant administration of PIPC might inhibit renal tubular secretion competitively, reducing the renal clearance of other antibiotics [29]. According to the Japanese package insert of PT, the incidence rate of AKI is 0.4%. However, an increasing rate of AKI in patients receiving PT monotherapy compared to that with CFPM monotherapy was reported in Japanese populations (8.6% vs 0.9%; OR [95% C·I.], 9.53 [1.41, 408]) [30]. Furthermore, in comparison to that with biapenem (a carbapenem-class agent), PT therapy induced AKI more frequently (11.3% vs 0%, $p = 0.005$) [31]. Another study corroborated that the renal recovery rate in patients treated with PT was lower than that in those treated with other β-lactams [32]. These facts suggest that PT alone might involve renal dysfunction, rather than VP combination therapy itself. In the meantime, PT administration could also increase SCr by inhibiting creatinine tubular secretion without reducing the glomerular filtration rate [33]. Therefore, an increase in SCr levels in patients administered PT might not necessarily indicate the incidence of AKI.

The nephrotoxic effects of VCM and PT combination might be additively associated with the incidence of AKI. A recent study showed that VP therapy could increase the release of AKI biomarkers such as urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor binding protein 7 [10]. In addition, a previous study demonstrated that AKI incidence is associated with an increase in the production of reactive oxygen species and oxidative stress, which is not observed with a higher VCM trough level alone [11] but can be enhanced by the simultaneous administration of VCM and β-lactams [3]. A further well-constructed

**Table 2**
Breakdown of antibiotics co-administered with vancomycin in VA therapy.

| Antibiotics | Number of patients (%) |
|---|---|
| *Anti*-pseudomonal agents | 68 (37.8) |
| Meropenem | 42 (23.3) |
| Cefepime | 14 (7.8) |
| Ceftazidime | 11 (6.1) |
| Aztreonam | 1 (0.6) |
| Antibiotics without *anti*-pseudomonal activity[a] | 141 |
| Ceftriaxone | 44 (24.4) |
| Ampicillin/Sulbactam | 35 (19.7) |
| Ampicillin | 24 (13.3) |
| Cefoperazone/Sulbactam | 19 (10.6) |
| Cefmetazole | 13 (7.2) |
| Cefotaxime | 2 (1.1) |
| Cefotiam | 2 (1.1) |
| Cefazolin | 2 (1.1) |

VA, vancomycin with another β-lactam.
[a] In case two and more antibiotics were given in a patient, all the agents were counted.

**Table 3**
Multivariate logistic regression analysis for the development of acute kidney injury.

| | Odds ratio (95% confidence interval) | *p* value |
|---|---|---|
| Male | 0.96 (0.47, 1.96) | 0.90 |
| Age | 1.01 (0.98, 1.04) | 0.55 |
| ICU admission when the combination was initiated | 0.40 (0.14, 1.17) | 0.09 |
| Sepsis (qSOFA≥2) | 2.39 (0.94, 6.06) | 0.07 |
| Concomitant nephrotoxins | 1.84 (0.84, 4.05) | 0.13 |
| Diabetes mellitus | 1.01 (0.39, 2.59) | 0.99 |
| VCM treatment duration | 1.01 (0.98, 1.04) | 0.47 |
| VCM initial trough levels ≥15 μg/mL | 3.19 (1.57, 6.48) | <0.01 |
| VCM combined with PT | 2.40 (1.20, 4.78) | 0.01 |

ICU, intensive care unit; qSOFA, quick sequential organ failure assessment; VCM, Vancomycin; PT, piperacilin/tazobactam.

**Table 4**
Univariate analysis for clinical characteristics and outcome of patients in general ward and intensive care unit treated with VP and VA therapy.

| | General ward (N = 198) | | | | Intensive care unit (N = 74) | | | |
|---|---|---|---|---|---|---|---|---|
| | VP (N = 69) | VA (N = 129) | *p* value | Odds ratio (95% CI) | VP (N = 23) | VA (N = 51) | *p* value | Odds ratio (95% CI) |
| Male (%) | 40 (58.0) | 75 (58.1) | 1 | 0.99 (0.53, 1.88) | 17 (73.9) | 34 (66.7) | 0.60 | 1.41 (0.43, 5.19) |
| Age [IQR], year | 77 [70.0, 85.0] | 76 [66.0, 83.0] | 0.26 | – | 80 [64.0, 83.5] | 74 [63.0, 82.5] | 0.43 | – |
| VCM treatment duration [IQR], days | 7 [4, 14] | 9 [4, 14] | 0.76 | – | 7 [5, 10.5] | 5 [4, 8] | 0.23 | – |
| Combination duration [IQR], days | 6 [4, 13] | 7 [4, 12] | 0.21 | – | 5 [4, 7] | 5 [4, 8] | 0.70 | – |
| Concomitant nephrotoxins (%) | 42 (60.9) | 85 (65.9) | 0.54 | 0.81 (0.42, 1.55) | 21 (91.3) | 37 (72.5) | 0.13 | 3.91 (0.78, 38.8) |
| Nosocomial infection (%) | 43 (62.3) | 70 (54.3) | 0.30 | 1.39 (0.74, 2.66) | 11 (47.8) | 17 (33.3) | 0.30 | 1.82 (0.59, 5.61) |
| Sepsis (qSOFA≥2) (%) | 9 (13.0) | 14 (10.9) | 0.65 | 1.23 (0.44, 3.26) | 19 (82.6) | 42 (82.4) | 1 | 1.02 (0.24, 5.10) |
| Comorbid conditions (%) | | | | | | | | |
| Malignancy | 26 (37.7) | 44 (34.1) | 0.64 | 1.17 (0.60, 2.24) | 8 (34.8) | 11 (21.6) | 0.26 | 1.92 (0.56, 6.50) |
| Diabetes mellitus | 12 (17.4) | 9 (7.0) | 0.03 | 2.79 (1.01, 7.97) | 11 (47.8) | 12 (23.5) | 0.06 | 2.93 (0.92, 9.55) |
| Chronic heart failure | 4 (5.8) | 8 (6.2) | 1 | – | 2 (8.7) | 3 (5.9) | 0.64 | – |
| COPD | 3 (4.3) | 6 (4.7) | 1 | – | 0 | 3 (5.9) | 0.55 | – |
| TDM analysis for VCM (%) | 65 (94.2) | 117 (90.7) | 0.59 | – | 20 (87.0) | 49 (96.1) | 0.17 | – |
| VCM initial trough level [IQR], μg/mL | 12.5 [9.7, 20.0] | 13.3 [9.5, 18.5] | 0.98 | – | 16.0 [12.1, 20.4] | 13.4 [8.7, 20.3] | 0.23 | – |
| VCM initial trough ≥15 μg/mL (%) | 25 (36.2) | 48 (37.2) | 1 | 0.96 (0.50, 1.83) | 11 (47.8) | 22 (43.1) | 0.80 | 1.21 (0.40, 3.63) |
| Development of AKI (%) | 18 (26.1) | 16 (12.4) | 0.02 | 2.48 (1.10, 5.67) | 5 (21.7) | 6 (11.8) | 0.30 | 2.06 (0.44, 9.30) |

VP, vancomycin with piperacillin/tazobactam; VA, vancomycin with another β-lactam; CI, confidential intervals; IQR, interquartile range; VCM, vancomycin; qSOFA, quick sequential organ failure assessment; COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury.
Continuous variables were compared by the Mann-Whitney *U* test and categorical variables were compared by the Fisher's exact tests. Odds ratios were calculated for the categorical variables.

study is warranted to clarify the AKI-associated mechanism underlying renal dysfunction with VP therapy.

Our univariate analysis revealed a significantly higher number of DM patients associated with VP therapy than with VA therapy. Since DM can be an independent risk factor for AKI [34], baseline comorbidity of DM in patients with VP therapy might be associated with the higher AKI incidence. Meanwhile, another study suggested that DM was not necessarily associated with the development of AKI among septic patients [35]. Based on the result of multivariate analysis in this study, DM was not considered as a risk factor of AKI when administering VP therapy (OR = 1.01).

Among ICU patients, although the incidence of AKI was relatively high with VP therapy, there was no significant difference between the two groups (21.7% vs 11.8%; $p = 0.30$). First, the small number of cases is possibly responsible for this result. ICU patients usually have many risk factors associated with AKI, and hence, factors other than the VP combination could affect AKI incidence. To further clarify the relevance of VP therapy to AKI, a well-designed, larger study is warranted. Second, the increased risk of AKI might not be true for critically-ill patients [12]. One study reported that a combination of VP was associated with no greater risk of moderate to severe AKI than VA (meropenem and CFPM) [6]. Even though the patients in that study received combination therapy for only up to 72 h, the outcome was consistent with our results. Third, in this study, ICU patients received shorter durations of VCM administration compared to GW patients ($p < 0.01$). Prolonged VCM treatment is one of the risk factors of increased AKI [36], and this difference could result in the occurrence of AKI.

In previous studies investigating the AKI incidence rate, β-lactams co-administered with VCM, compared to VP therapy, were *anti*-pseudomonal agents, such as CFPM or carbapenems [5,6,8,9,11]. In our study, only 37.8% (68/180) of patients administered VA therapy were administered β-lactams with *anti*-pseudomonal activity. Although the clinical backgrounds of patients in the VA and VP therapy groups in the present study were almost identical (except DM as a comorbid condition), the prognoses of infections associated with non-fermentative gram-negative bacilli such as *Pseudomonas aeruginosa* are generally worse [37]. Therefore, there is a concern that the populations in this study could be different from those in previous literature. However, our data might indicate that VA therapy without *anti*-pseudomonal agents would also be safer than VP therapy.

Several limitations of our study should be considered. First, this was a single-centered retrospective study without randomization of patient selection, and there might be several confounding factors affecting the statistical results. Second, we excluded patients whose baseline SCr was >1.2 mg/dL based on a preceding study [11] and those who required hemodialysis when receiving combination therapies. Baseline renal failure was reported as an independent risk factor for VCM-induced nephrotoxicity [3]. Therefore, further investigations focusing on patients with renal dysfunction would be needed in the future. Third, TDM analysis for VCM was not

performed for all patients. As a high trough level of VCM alone is an independent risk factor of AKI [24], the incompleteness of these data might have skewed the results. As TDM analysis can increase drug effectiveness and decrease the risk of AKI, it is necessary to conduct TDM especially when the VCM treatment duration is longer [38]. Forth, SCr elevation alone could be an insufficient marker of AKI development. As pointed out recently [39], SCr is a surrogate marker of glomerular function, but does not necessarily directly indicate renal injury. The administration of PT inhibits creatinine tubular secretion, yielding an increase in SCr [33], which makes it appear that PT causes AKI directly. Older patients, particularly those who are in malnutrition states, have lower body muscle mass, which influences the SCr level in a condition of renal dysfunction. Although Cystatin C, a novel biomarker of AKI, might be alternatively applied [40], its validity in evaluating AKI is yet to be established. Referring to previous studies [5–11], we assessed SCr in this study.

In summary, combination therapy of VCM with PT was associated with an increased incidence of AKI in Japanese populations. As both empiric and definitive therapies, these antimicrobial agents are frequently co-administered to patients. To avoid AKI, it might be necessary to choose β-lactam antibiotics rather than PT for combinations with VCM treatment.

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## Authorship statement

All authors meet the ICMJE authorship criteria, in that all authors made substantial contributions to the conception and design of the study, acquisition of data, or analysis and interpretation of data. In additional, all authors were involved in drafting the manuscript or revising it critically for important intellectual content, and all provided final approval of the version to be submitted.

## Declaration of competing interest

None.

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