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Original Article

Concomitant Use of Multiple Nephrotoxins Including Renal Hypoperfusion Medications Causes Vancomycin-Associated Nephrotoxicity: Combined Retrospective Analyses of Two Real-World Databases

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There is a growing concern about the relationship between vancomycin-associated nephrotoxicity (VAN) and concomitant use of nephrotoxins. We examined this relationship by combined retrospective analyses of two real-world databases. Initially, the FDA Adverse Event Reporting System (FAERS) was analyzed for the effects of concomitant use of one or more nephrotoxins on VAN and the types of combinations of nephrotoxins that exacerbate VAN. Next, electronic medical records (EMRs) of patients who received vancomycin (VCM) at Tokushima University Hospital between January 2006 and March 2019 were examined to confirm the FAERS analysis. An elevated reporting odds ratio (ROR) was observed with increases in the number of nephrotoxins administered (VCM + one nephrotoxin, adjusted ROR (95% confidence interval [CI]) 1.67 [1.51-1.85]; VCM + ≥ 2 nephrotoxins, adjusted ROR [95% CI] 1.54 [1.37-1.73]) in FAERS. EMRs analysis showed that the number of nephrotoxins was associated with higher incidences of VAN [odds ratio: 1.99; 95% CI: 1.42-2.78]. Overall, concomitant use of nephrotoxins was associated with an increased incidence of VAN, especially when at least one of those nephrotoxins was a renal hypoperfusion medication (furosemide, non-steroidal anti-inflammatory drugs, and vasopressors). The concomitant use of multiple nephrotoxins, especially including renal hypoperfusion medication, should be avoided to prevent VAN.

Key words: vancomycin-associated nephrotoxicity, polypharmacy, nephrotoxin, spontaneous adverse event reporting database, electronic medical records

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Vancomycin (VCM) is a glycopeptide antimicrobial agent used as a first-line intravenous drug for infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [1-3]. Vancomycin-associated nephrotoxicity (VAN) is a severe adverse event with an incidence of approximately 5-43% in patients receiving a VCM regimen [1,2,4]. Moreover, the mortality rate associated with VAN has been reported at 15-20% [5,6]. Thus, it is important to prevent VAN by examining its diverse risk factors, including patient-related factors (*e.g.*, age and body weight), VCM-related factors (*e.g.*, dose and concentration), and medication-related factors (*e.g.*, concomitant use of nephrotoxins such as aminoglycosides, furosemide, liposomal amphotericin B, nonsteroidal anti-inflammatory drugs (NSAIDs), piperacillin/tazobactam, vasopressors, and intravenous contrast) [1,3,7,8].

To date, increases in the prevalence of polypharmacy, defined as the prescription of five or more drugs, has led to growing concerns about the consequences of increased nephrotoxin administration [9]. Polypharmacy is a risk factor for acute kidney injury caused by administration of antibiotics [10]. Therefore, it is essential to be cautious about the increased risk of developing VAN with the concomitant use of one or more nephrotoxins. The concomitant use of VCM with renal hypoperfusion medications (*e.g.*, NSAIDs, and diuretics), which are considered nephrotoxins, is associated with an increased risk of kidney injury [11] and VAN [12]. Therefore, it is important to examine the effect of concomitant use of other nephrotoxins, especially in combination with renal hypoperfusion medications, on the development of VAN.

Decisions about VCM therapy in patients with concomitant use of nephrotoxins should be based on data. Recently, real-world data from spontaneous reporting databases and electronic medical records (EMRs) have been extensively used in identifying adverse events related to polypharmacy [13,14]. However, both types of databases have limitations in extracting accurate safety information when analyzed alone [15,16]. The combined analyses of spontaneous reporting databases with other types of real-world databases produces stronger evidence in clinical studies [17-23]. The aim of the present study was to examine the effect of the concomitant use of one or more nephrotoxins in the development of VAN using the combined analysis of two different-type real-world databases.

Materials and Methods

Combined analyses using two databases, the FDA Adverse Events Reporting System (FAERS) and EMRs from a single university hospital, was utilized to examine the association between the occurrence of VAN and concomitant use of multiple nephrotoxins (Fig. 1). First, we examined the trends in the number of administered drugs and nephrotoxins stratified by age in the FAERS. Second, we conducted combined analyses of the FAERS and EMR to examine the association between VAN and the concomitant use of nephrotoxins, and to identify the combinations of nephrotoxins that exacerbate VAN. The analysis of EMRs was approved by the Ethics Committee of Tokushima University Hospital (reference number 3,431) and conducted according to the Declaration of Helsinki. The Ethics Committee waived the need for informed consent since this was an observational study using existing data. With respect to the analysis of the FAERS database, institutional review board approval was not required owing to the anonymized nature of the open-access data.

Study population

1. FAERS analysis. Adverse event reports were downloaded from the FDA website <https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html>, (accessed 14 April 2020). Data from the first quarter of 2004 to the first quarter of 2020 in the FAERS were analyzed. In the case of duplicate reports, only the most recent report was used for analysis, as recommended by the FDA. Only reports that contained complete age information were extracted. We limited our analysis to patients aged 18 years or older, and those who received VCM intravenously.

2. EMRs analysis. A retrospective case-control study was performed using EMRs from the Tokushima University Hospital in Tokushima, Japan. The inclusion criteria were patients who received VCM between January 2006 and March 2019. The exclusion criteria were patients who (1) received VCM treatment for < 48 h; (2) did not undergo therapeutic drug monitoring (TDM) of VCM; (3) were under 18 years of age; or (4) had prior acute kidney injury (AKI) or renal dysfunction. After exclusion of patients with the above-mentioned criteria and insufficient clinical data, 504 patients were enrolled in this study.

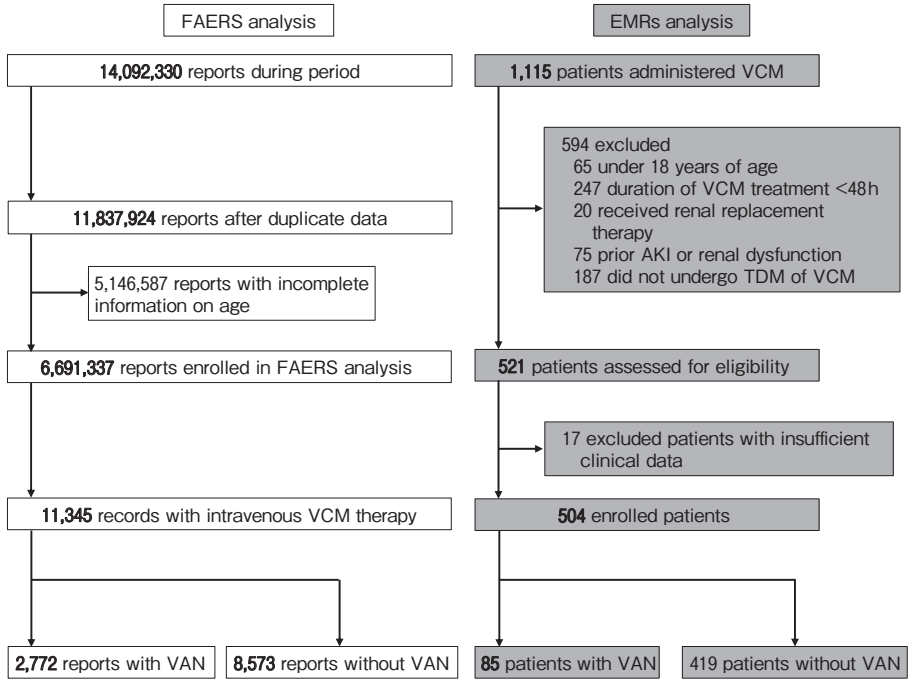

Fig. 1 Flow diagram of the study design.
EMRs, electronic medical records; FAERS, FDA Adverse Events Reporting System; TDM, therapeutic drug monitoring; VCM, vancomycin; VAN, vancomycin-associated nephrotoxicity.

Data collection and definitions

1. FAERS analysis

The description of adverse events conforms to the Medical Dictionary for Regulatory Activities (MedDRA/ver. 23.1) developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Therefore, adverse events were defined using MedDRA-conforming adverse event terminology. VAN was defined by 47 preferred terms in the standardized MedDRA queries under "acute renal failure" (SMQ 20000003) according to a previous report [18]. The only exceptions were "fetal" and "neonatal" as a search term in reports of patients who received VCM (Table 1). Seven drugs or drug types were defined as a nephrotoxins previously shown to increase the risk for the occurrence of VAN: aminoglycosides, furosemide, intravenous contrast, liposomal amphotericin B, NSAIDs, piperacillin/tazobactam, and vasopressors [1,7]. Among these, furosemide, NSAIDs, and vasopressors decrease renal blood flow, and were defined as renal hypoperfusion medications [12,24].

2. EMRs analysis

Data on laboratory results and disease history were collected at the initial administration of VCM as the baseline data. We defined VAN as an increase in serum creatinine (SCr) level by ≥0.5 mg/dL (44.2 μmol/L) or as a 50% or more increase from the baseline SCr level, for ≥2 consecutive days from the start to 72 h after VCM administration [5,25]. Nephrotoxins, renal hypoperfusion medications, and other medications in the EMRs were defined according to the criteria described above. In patients without VAN, concomitant use of nephrotoxins was defined as the use of any of the aforementioned nephrotoxins at least from the beginning of administration to 72 h after VCM administration (Fig. 2) [1,5]. In patients with VAN, concomitant use of nephrotoxins was defined as the use of any nephrotoxin from the beginning of VCM administration (or earlier) up to the occurrence of VAN. In patients without VAN, the average VCM trough level during VCM therapy was used for analysis; in patients with VAN, the average VCM trough level before the occurrence of VAN was used for analysis. The average trough level was utilized as an indicator of VCM expo-

Table 1 Forty-seven preferred terms of acute renal failure

Acute kidney injury	Creatinine renal clearance decreased	Intradialytic parenteral nutrition	Renal function test abnormal
Acute phosphate nephropathy	Creatinine urine abnormal	Kidney injury molecule-1	Renal impairment
Albuminuria	Creatinine urine decreased	Nephritis	Renal transplant
Anuria	Crystal nephropathy	Nephropathy toxic	Renal tubular disorder
Azotaemia	Dialysis	Neutrophil gelatinase-associated lipocalin increased	Renal tubular dysfunction
Blood creatinine abnormal	Fractional excretion of sodium	Oedema due to renal disease	Renal tubular injury
Blood creatinine increased	Glomerular filtration rate abnormal	Oliguria	Renal tubular necrosis
Blood urea abnormal	Glomerular filtration rate decreased	Peritoneal dialysis	Subacute kidney injury
Blood urea increased	Haemodialysis	Prerenal failure	Tubulointerstitial nephritis
Blood urea nitrogen/creatinine ratio increased	Haemofiltration	Protein urine present	Urea renal clearance decreased
Continuous haemodiafiltration	Hypercreatininaemia	Proteinuria	Urine output decreased
Creatinine renal clearance abnormal	Hyponatriuria	Renal failure	

sure because it is a reasonable risk factor for the development of VAN. Prior AKI in this study was defined by referring to the Kidney Disease: Improving Global Outcome (KDIGO) Clinical Practice Guideline for Acute Kidney Injury, as follows: (1) an increase in SCr level to ≥1.5 times that of the baseline level known or presumed to have occurred in the previous 7 days; or (2) an increase in SCr level by ≥0.3 mg/dL (26.5 μmol/L) within 48 h before or after VCM administration [5,26]. Hypoalbuminemia was defined as an albumin level of <3.5 g/dL [27]. The estimated glomerular filtration rate (eGFR) was calculated using the following formula: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (for females) [28].

Statistical analysis. Differences between two groups were analyzed using either the parametric unpaired *t*-test or non-parametric Mann–Whitney *U* test. Categorical variables were compared using Fisher's exact test or the chi-squared test. Significant differences in categorical variables among three groups were determined using Fisher's exact test followed by Bonferroni multiple comparisons. Multiple logistic regression analysis was used to examine the independent variables posing risk for the development of VAN. In FAERS analysis, signal detection for the risk of adverse events was assessed via a disproportionality analysis using the reported odds ratio (ROR) and 95% confidence interval (CI). A risk signal was considered significant when the ROR and the lower limit of the corresponding 95% CI was >1 [18,19]. Adjusted ROR was calculated after adjustments for sex and age. The *a priori* selection of variables during EMRs analysis was based on published literature that examined risk factors for the development of VAN; these variables included age, ICU admission, daily dose of VCM, and an average VCM trough level ≥20 mg/L [7,25,29]. Candidate factors were selected by considering multicollinearity among those meeting the $p < 0.05$ criteria in a two-group comparison with *a priori* factors. The results of regressions are reported as partial regression coefficients and 95% CIs. *P*-values <0.05 were considered statistically significant. Data are shown as means (standard deviations) or medians (IQRs). Statistical analysis was performed using JMP® 15.0 software (SAS Institute Inc., Cary, NC, USA).

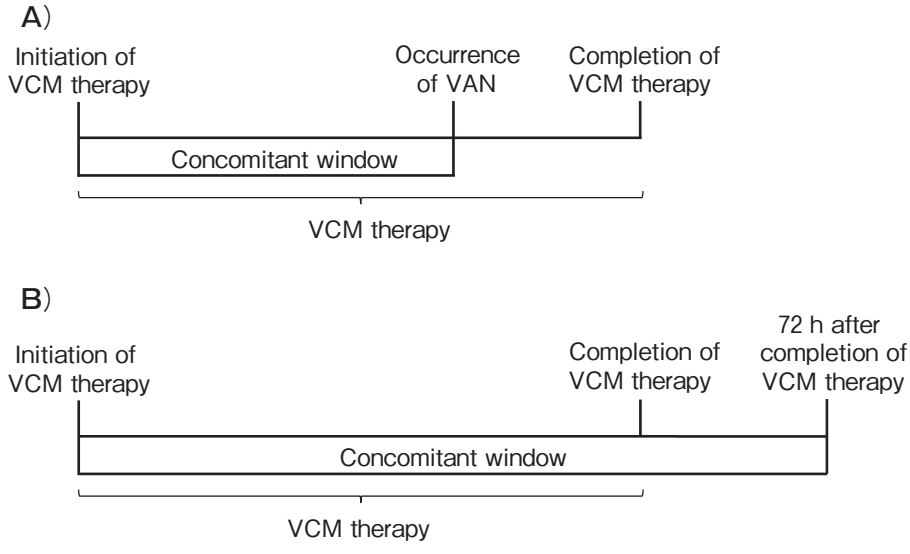

Fig. 2 Illustration of the definition of concomitant nephrotoxins used in analysis of EMRs. **A**) A Case with VAN, **B**) A case without VAN. **A**) In cases with VAN, if a nephrotoxin was administered from the start of VCM to the occurrence of VAN, the case was determined as a case with concomitant use of nephrotoxins. **B**) In cases without VAN, if a nephrotoxin is administered from the start of VCM to 72h after completion of VCM therapy, the case was determined as a case with concomitant use of nephrotoxins.
EMRs, electronic medical records; VCM, vancomycin; VAN, vancomycin-associated nephrotoxicity. The number of concomitant nephrotoxins was defined as the number of nephrotoxins other than VCM used during the window of VCM.

Results

Population in the FAERS and EMRs

1. FAERS analysis

During the study period, the FAERS received 14,092,330 spontaneous adverse event reports. After excluding duplicate data and reports without complete information on age, the remaining 6,691,337 reports were analyzed. Out of these reports, 11,345 cases received VCM, and 2,772 cases (24.4%) were classified as having developed VAN (Fig. 1).

2. EMRs analysis

During the study period, VCM was administered to a total of 1,115 patients at Tokushima University Hospital, 504 of whom were enrolled after applying the exclusion criteria. Among them, 85 patients (16.9%) developed VAN (Fig. 1).

Trends on the number of administered drugs stratified by age in FAERS

Among 6,691,337 reports, the proportion of patients receiving polypharmacy (*i.e.*, being treated with more than five drugs) was 17.9% in the 20-29 age group. This gradually increased by age group, reaching a maximum of 39.5% in the ≥90 years age group (Fig. 3A). In contrast, that of single drug use decreased from 44.6% in the 20-29 age group to 31.0% in the ≥90 group (Fig. 3A). The proportion of patients who received more than two nephrotoxins (multiple nephrotoxins) increased from 4.4% in the 20-29 group to 18.1% in the ≥90 group (Fig. 3B).

Association between VAN occurrence and number of concomitant nephrotoxins in FAERS and the EMRs

1. FAERS analysis

We compared the characteristics of 11,345 patients with and without VAN that were administered VCM in the FAERS. There were significant differences in sex, age, and number of concomitant nephrotoxins administered and concomitant agents for renal hypoperfusion between the two groups ($p < 0.001$) (Table 2). Therefore, we evaluated the ROR of VAN with concomitant use of nephrotoxins. The crude and adjusted ROR of VCM-associated AKI are summarized in Table 3. The adjusted ROR for VCM + one nephrotoxin, VCM + ≥2 nephrotoxins were 1.67 (1.51-1.85) and 1.54 (1.37-1.73), respectively (Table 3A). Similarly, the adjusted ROR for VCM + one agent for renal hypoperfusion, VCM + ≥2 agents for renal hypoperfusion were 1.50 (1.36-1.67) and 2.26 (1.93-2.66), respectively (Table 3B).

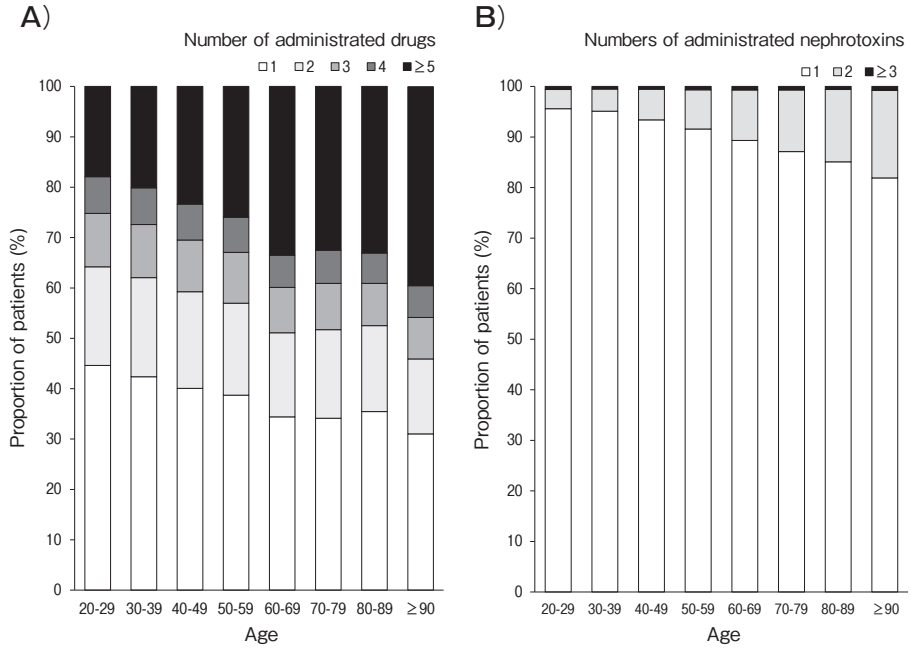

Fig. 3 Proportion of reports by number of administered drugs stratified by age in the FAERS.
A) Proportion of reports by number of administered drugs stratified by age in the FAERS. **B**) Proportion of reports by number of administered nephrotoxins stratified by age in the FAERS.
FAERS, FDA Adverse Events Reporting System.

Table 2 Clinical characteristics in cases with and without VAN in the FAERS

	Without VAN (N = 8573)	With VAN (N = 2772)	*P*-value
Sex			
Female	3,812 (44.5%)	1,089 (39.3%)	< 0.001
Male	4,695 (54.8%)	1,648 (59.5%)	
Unknown	66 (0.8%)	35 (1.3%)	
Age (year)	60.0 (48.0–71.0)	62.0 (51.0–73.0)	< 0.001
Number of concomitant nephrotoxins	0 (0–1)	1 (0–2)	< 0.001
Number of concomitant agents for renal hypoperfusion	0 (0–1)	0 (0–1)	< 0.001

Values for categorical variables are given as count (%) and for continuous variables as median (interquartile range).
VAN, vancomycin-associated nephrotoxicity; FAERS, FDA Adverse Events Reporting System.

2. EMRs analysis

Patient characteristics were also compared between the two groups with and without VAN in the EMRs analysis. There were significant differences in sex, daily dose of VCM, the number of concomitant nephrotoxins and concomitant agents for renal hypoperfusion administered, the number of patients with an average VCM trough level ≥ 20 mg/L, and hypoalbuminemia between the two groups ($p < 0.05$) (Table 4). Therefore, these factors were selected as candidates for explanatory variables in the multivariate analysis while considering multicollinearity. The development of VAN was associated with an average VCM trough level ≥ 20 mg/L (OR, 2.75; 95% CI, 1.62-4.67), hypoalbuminemia (OR, 2.26; 95% CI, 1.04-4.95), and increased the number of concomitant nephrotoxins (OR, 1.99; 95% CI, 1.42–2.78) (Fig. 4). Similarly, the number of renal hypoperfusion agents used concomitantly was associated with the development of VAN (OR, 1.92; 95% CI, 1.19-3.09) when it was used as the explanatory variable instead of

Table 3 Signals of VCM-associated AKI in cases with concomitant nephrotoxins and agents for renal hypoperfusion

A) Signals of VCM-associated AKI in the cases with concomitant nephrotoxins

	Cases with AKI	Cases without AKI	Crude ROR (95%CI)	Adjusted ROR (95%CI)
VCM	1,074	4,764	1 (Reference)	1 (Reference)
VCM + one nephrotoxin	923	2,460	1.66 (1.50–1.84)	1.67 (1.51–1.85)
VCM + ≥2 nephrotoxins	775	1,349	1.53 (1.36–1.72)	1.54 (1.37–1.73)

B) Signals of VCM-associated AKI in cases with concomitant agents for renal hypoperfusion

	Cases with AKI	Cases without AKI	Crude ROR (95% CI)	Adjusted ROR (95% CI)
VCM	1,691	6,398	1 (Reference)	1 (Reference)
VCM + one agent for renal hypoperfusion	675	1,718	1.49 (1.34–1.65)	1.50 (1.36–1.67)
VCM + ≥2 agents for renal hypoperfusion	406	457	2.26 (1.93–2.66)	2.26 (1.93–2.66)

ROR in cases with VCM + ≥2 Nephrotoxins was calculated as ROR to cases with VCM + one nephrotoxin.
AKI, acute kidney injury; ROR, reporting odds ratio; VCM, vancomycin.

Table 4 Clinical characteristics in patients with and without VAN in EMRs from Tokushima University Hospital

	Without VAN (N = 419)	With VAN (N = 85)	*P*-value
Sex (Male/Female)	275/144	46/39	0.048
Age (year)	65.8 (55.1–73.8)	63.7 (55.6–69.4)	0.125
ICU admission	55 (13.1%)	17 (20.0%)	0.124
Daily dose of VCM (mg/kg/day)	20.4 (15.1–33.1)	23.2 (17.9–37.8)	0.016
Average VCM trough level (mg/L)	11.0 (7.50–16.0)	17.2 (12.4–24.5)	<0.001
Average VCM trough level ≥20 mg/L	69 (16.5%)	35 (41.2%)	<0.001
Length of vancomycin therapy (day)	9.0 (6.0–13.0)	9.0 (6.5–13.0)	0.964
eGFR (mL/min/1.73 m^2)	72.0 (54.2–100.0)	79.1 (57.1–114.3)	0.082
eGFR <60 mL/min/1.73 m^2	61 (17.6%)	24 (15.3%)	0.608
Hypoalbuminemia	334 (79.7%)	76 (89.4%)	0.046
Complication disease			
Hypertension	151 (36.0%)	23 (27.1%)	0.133
Diabetes	165 (39.4%)	24 (28.2%)	0.065
Chronic heart failure	57 (13.6%)	12 (14.1%)	0.864
Chronic kidney disease	24 (5.7%)	4 (4.7%)	1.000
Cancer	258 (61.6%)	49 (57.7%)	0.543
Stroke	22 (5.3%)	6 (7.1%)	0.447
Infection site			
Abdomen	28 (6.7%)	8 (9.4%)	0.359
Bone	10 (2.4%)	1 (1.2%)	0.700
Catheter-related	11 (2.6%)	2 (2.4%)	1.000
Central nervous system	21 (5.0%)	4 (4.7%)	1.000
Respiratory tract	74 (17.7%)	17 (20.0%)	0.643
Urinary tract	16 (3.8%)	2 (2.4%)	0.750
Number of concomitant nephrotoxins	0 (0–1)	1 (0–1)	<0.001
Number of concomitant agents for renal hypoperfusion	0 (0–0)	0 (0–1)	<0.001

eGFR, estimated glomerular filtration rate; ICU, intensive care unit; VAN, vancomycin-associated nephrotoxicity; EMRs, electronic medical records; VCM, vancomycin.

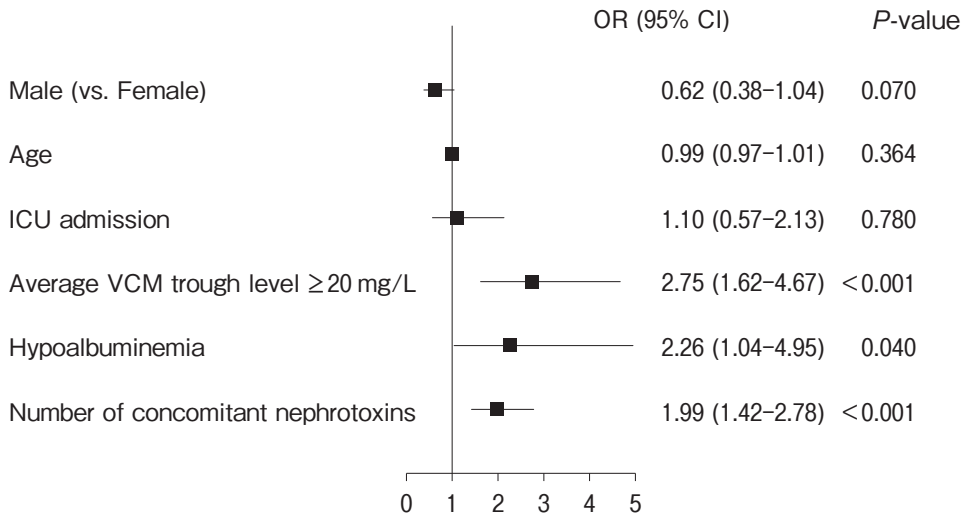

Fig. 4 Analysis of factors influencing the incidence of VAN in the EMRs.
EMR, electronic medical records; ICU, intensive care unit; VCM, vancomycin; VAN, vancomycin-associated nephrotoxicity.

the number of nephrotoxins used concomitantly in the multivariate analysis (data not shown).

These results, using combined analyses of FAERS and one hospital's EMR, showed that the number of concomitant nephrotoxins administered was associated with the development of VAN.

Association between VAN and concomitant renal hypoperfusion medication in combined analysis of the FAERS and EMRs. We examined the relationship between concomitant use of renal hypoperfusion medications and the development of VAN stratified by the number of nephrotoxins used concomitantly, based on the above-mentioned FAERS and EMR analysis. FAERS analysis showed that there were significant differences in the reporting rate of VAN between the two groups (with and without renal hypoperfusion medications) when more than two nephrotoxins were used in combination [with renal hypoperfusion medications, 38.6% (687/1780); without renal hypoperfusion medications, 25.6% (88/344); $p<0.001$] but not in the group with use of a single nephrotoxin [with renal hypoperfusion medications, 26.7% (395/1477), without renal hypoperfusion medications, 27.7% (528/1906); $p=0.56$] (Fig. 5). EMRs analysis showed that the incidence of VAN in the group which received two or more nephrotoxins including at least one renal hypoperfusion medication was likely to be higher that without renal hypoperfusion medications [with renal hypoperfusion medications; 42.1% (8/19), without renal hypoperfusion medications 18.2% (4/22); $p=0.17$] (Fig. 5). These results suggest that the risk of development of VAN is increased when multiple nephrotoxin administration includes at least one renal hypoperfusion medication.

Discussion

This study clearly demonstrated a positive association between the number of nephrotoxins and the risk of developing VAN through combined analyses of FAERS and a university hospital EMR. The results suggest that the concomitant use of multiple (≥ 2) nephrotoxins, especially when at least one is a renal hypoperfusion medication is related to an increased risk for VAN. Previous reports studied the association between the increased risk for VAN and concomitant use of each nephrotoxin class, whereas the relationship between the occurrence of VAN, the concomitant use of multiple nephrotoxins, and the combination of nephrotoxins that exacerbate VAN were not examined [1,3,7,8]. The novel findings of the present study provide useful information on the risks of VCM therapy with multiple nephrotoxins in a situation where polypharmacy is becoming more prevalent.

The number of renal hypoperfusion medications such as NSAIDs and diuretics has been shown to be associated with the occurrence of kidney injury [11]. The combination of two hypoperfusion medications with valacyclovir was shown to increase the risk of

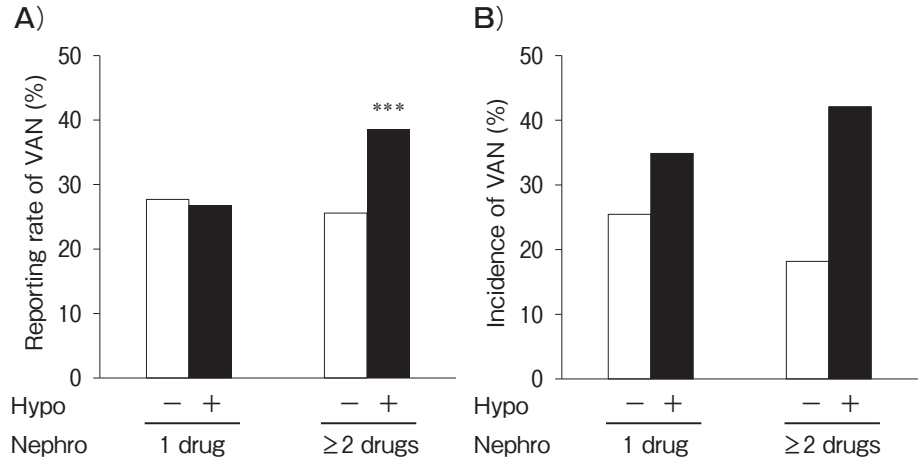

Fig. 5 Effect of concomitant use of renal hypoperfusion medications on the incidence of VAN stratified by the number of nephrotoxins including hypoperfusion medications. **A**) Analysis of the FAERS: Reporting rates of VAN were compared between the groups receiving renal hypoperfusion medications and those not receiving them in the group with one nephrotoxin and the group with two or more nephrotoxins, respectively, **B**) EMRs analysis; Incidence of VAN were compared between the groups receiving renal hypoperfusion medications and those not receiving them in the group with one nephrotoxin and the group with two or more nephrotoxins, respectively.
FAERS, FDA Adverse Events Reporting System; EMRs, Electronic medical records; Hypo, renal hypoperfusion medications; Nephro, the number of concomitantly used nephrotoxins; VAN, vancomycin-associated nephrotoxicity.
***: $P<0.001$; versus the group not receiving renal hypoperfusion medications in cases with two or more nephrotoxins.

developing valacyclovir-associated kidney injury, a well-known drug-induced kidney injury, more than the combination of one such drug with valacyclovir [30]. These results are consistent with the positive association revealed in the present study between the number of administered nephrotoxins and the risk of occurrence of VAN, and suggest that the decision to initiate VCM therapy must be carefully considered in those with concomitant use of multiple nephrotoxins. NSAIDs decrease urinary output via arteriole constriction in the glomerulus [31]. Cisplatin-related nephrotoxicity, which is a common drug-induced kidney injury caused by the injury of proximal tubules, is accelerated by an increase in serum cisplatin concentration due to a decrease in the glomerular filtration rate (GFR) with lower blood pressure [32]. VCM causes nephrotoxicity through proximal tubular injury similar to cisplatin [33, 34]. The increased risk for VAN is associated with a decreased GFR from the concomitant use of renal hypoperfusion medications [12]. Diuretics, one of the groups of renal hypoperfusion medications, decrease GFR through hypovolemia, which induces increased VCM trough concentration and is a major risk factor for VAN [35]. Our results also revealed that a high VCM trough concentration poses a risk factor for VAN. Thus, the concomitant use of renal hypoperfusion medications increase the serum concentration of any other nephrotoxins, suggesting one reason for the positive association between the number of nephrotoxins and the risk for VAN. Furthermore, our analysis of FAERS data showed the association between an increase in the proportion of use of concomitant multiple nephrotoxins and aging. Therefore, it is necessary to carefully monitor for the occurrence of VAN when multiple nephrotoxins are being administered in elderly patients or to hold off using routinely administered nephrotoxins such as furosemide when VCM therapy is deemed necessary. The use of multiple nephrotoxins, especially combinations including renal hypoperfusion medications, should be carefully considered before VCM therapy.

Although the features of the two methodologies complemented each other, there were several limitations inherent to each methodology. First, the category of nephrotoxins was limited to those drugs that have been clearly reported to increase the risk of developing VAN in FAERS- and/or EMR-based studies. Therefore, our results should be generalized carefully in patients receiving combination therapy with other potential nephrotoxins that were not defined as nephrotoxins

herein. Second, the analysis periods of the FAERS and EMR studies were different. This may have affected the overall results. Third, the FAERS data are known to have duplicate reports and significant amounts of missing data. To address this, duplicate reports were removed and only cases with sufficient information were selected. This may affect the results of the FAERS analysis, including the ROR. Fourth, there is no definitive proof of causality between VCM administration and the occurrence of so-called "VAN". Acute renal failure and its symptoms might have been caused by other unreported determinants. Therefore, the relationship between the occurrence of VAN and an increase in the number of nephrotoxins suggested by the current FAERS analysis should be interpreted with caution. The EMR database is more reliable compared to FAERS and was used in a robust retrospective case-control study design to address some of the limitations of FAERS analysis. The relationship between the occurrence of VAN and increased mortality — as suggested by FAERS analysis — was confirmed using multiple logistic regression analysis while adjusting for the confounding factors. However, this is a retrospective observational study. Due to the limited sample size, our results may not have fully accounted for all clinical factors associated with kidney failure in the context of vancomycin administration. A further study with a larger population concomitantly using multiple nephrotoxins is required to determine which combinations of nephrotoxins worsen VAN because of the limited cases in the present study with concomitant use of each type of nephrotoxin.

In conclusion, combined analyses of the spontaneous reporting database and EMRs from a single university demonstrated the association between the increased number of nephrotoxins and the occurrence of VAN. Our results indicated that the risk for VAN increases when a renal hypoperfusion agent is at least one of multiple nephrotoxins used concomitantly with VCM. The combination of nephrotoxins and VCM should be performed with careful consideration of overall patient safety.

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