Title

Comparison of the incidence of nausea and vomiting between linezolid and vancomycin using a claims database: a retrospective cohort study

Abstract

Background Nausea and vomiting during linezolid therapy have been reported as part of safety analyses in clinical trials. We have previously examined the incidence of vomiting during linezolid therapy (18.1%). A previous study conducted at a single hospital showed low external validity. It is necessary to verify whether these results can be reproduced using generalizable data sources.

Aim To evaluate the incidence of nausea and vomiting during linezolid therapy compared with vancomycin using a Japanese claims database.

Method Patients administered linezolid or vancomycin were selected from the database between January 2005 and June 2017. The primary endpoint was the comparison of nausea and vomiting between the linezolid and vancomycin groups. We conducted propensity score matching (PSM) to adjust for patient characteristics. To assess risk factors for nausea and vomiting, logistic regression was conducted as the secondary endpoint. We defined nausea and vomiting as the first prescription of antiemetics during linezolid or vancomycin therapy as a surrogate endpoint.

Results In total, 1,215 patients were enrolled. After PSM, the number of patients in the linezolid and vancomycin groups was 241. Nausea and vomiting were observed in 11.2% and 5.0% of patients in the linezolid and vancomycin groups, respectively ($p < 0.05$). Linezolid administration was extracted as a risk factor for nausea and vomiting (odds ratio, 2.09;

95% confidence interval, 1.02–4.30).

Conclusion This study clarified the relationship between linezolid and nausea and vomiting using a Japanese claims database. Further studies are required to elucidate the unknown mechanisms of linezolid-induced nausea and vomiting.

Impact statements

- This study using Japanese administrative claims database revealed that linezolid might be associated with nausea and vomiting.
- Clinicians and pharmacists should perform careful monitoring of occurrence of nausea and vomiting during linezolid therapy.
- Further studies are needed to identify the mechanism of linezolid induced nausea and vomiting, because the mechanism is unknown.

Introduction

Linezolid is an antibiotic used to treat methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. Because of its good penetration into organs and tissues, it is widely used to treat not only bacteremia and pneumonia but also skin, soft tissue, bone, and joint infections [1–3]. Some reports have described nausea and vomiting during linezolid administration. A safety analysis of a phase III study comparing the efficacy of linezolid with tedizolid reported that the incidence of linezolid-related nausea and vomiting was 12.2% and 5.6%, respectively [4]. Another pooled analysis of phase III studies that compared linezolid with other antimicrobial agents reported an incidence of nausea and vomiting of 3.4%

and 1.1%, respectively, in patients receiving linezolid [5]. In our previous reports, the incidence of vomiting was 18.1–23.4% during linezolid administration [6, 7], which was higher than that in clinical studies [4, 5]. Differences in the incidence of vomiting between the clinical studies and our previous studies may be due to differences in the patients' baseline characteristics.

The gold standard of clinical trials is a randomized controlled trial (RCT) with strict inclusion and exclusion criteria, whereas in clinical settings, many patients do not meet these criteria. In addition, RCTs on linezolid did not mention renal function in detail because the linezolid dosage does not need to be adjusted according to renal function. [8, 9] However, the linezolid blood concentration is elevated in patients with impaired renal function or low body weight and increases the frequency of hematological side effects, such as thrombocytopenia [10–12]. Therefore, the adverse effects of linezolid in clinical settings may differ from those previously reported in RCTs.

We examined the causal relationship between linezolid administration and the occurrence of vomiting and the risk factors for vomiting. However, because the previous study was conducted using the medical records of orthopedic patients from a single center, it did not show whether linezolid administration is generally associated with nausea and vomiting. Therefore, additional studies are crucial to validate the result of the previous study using real-world data. In recent years, research using real-world data, which is a collection of information on a large number of patients, has attracted attention and is being applied to post-marketing safety studies, revision of guidelines, and development of new drugs [13, 14].

Aim

This study aimed to verify the causal relationship between linezolid administration and nausea and vomiting to ensure

external validity using a Japanese claims database. We also compared the incidence of these events between the linezolid and vancomycin groups.

Ethics approval

This retrospective cohort study used a claims database from the Japan Medical Data Center (JMDC) Inc. The JMDC claims database contains complete anonymized data that cannot be coupled with personal information. The institutional review board of the Faculty of Pharmaceutical Sciences of Hokkaido University confirmed that no ethical approval was required.

Method

Study design

A retrospective cohort study using a claims database was conducted.

Database

We used the Japanese claims database provided by JMDC Inc. [15]. The JMDC claims database is a complex of anonymous data from 13,000,000 company employees belonging to health insurance associations. The database contains complete information on inpatient, outpatient, and pharmacy claims of patients aged < 75 years. Diagnosis, prescription drugs, and treatments were recorded using the International Classification of Diseases 10th Revision (ICD-10), Anatomical Therapeutic Chemical Classification System (ATC), and procedure codes, respectively.

77

78 **Study patients**

79 The inclusion criteria were patients treated with linezolid or vancomycin for the first time from January 2005 to June
80 2017. Patients who were administered linezolid or vancomycin were defined as the linezolid or vancomycin groups,
81 respectively. Linezolid and vancomycin were defined using ATC codes (Table 1S in the supplementary material). To avoid
82 significant reduction in sample size when excluding patients administered linezolid followed by vancomycin, patients who
83 received both drugs rather than combination therapy during the study period were considered to be in the linezolid group.
84 Linezolid was administered twice daily orally or intravenously at a fixed dose of 600 mg. Vancomycin was administered
85 intravenously, and the dose was not fixed because it was usually modified by therapeutic drug monitoring [16].

86 We excluded patients under 18 years old because the clearance of linezolid is negatively correlated with age in children
87 and may show different pharmacokinetic and side-effect profiles than in adults [17]. Patients prescribed antiemetics (i.e.,
88 metoclopramide, domperidone, and prochlorperazine) from 7 days prior to antimicrobial treatments were excluded because
89 they might have had nausea and vomiting unrelated to the antimicrobial treatments. To rule out confounding effects as
90 much as possible, we excluded patients with concomitant use of drugs that pharmacologically interact with linezolid (i.e.,
91 serotonergic agents, rifampicin, and monoamine oxidase inhibitors), opioids, dopamine type 2 blockers, NK-1 receptor
92 antagonists, and 5-HT type 3 receptor antagonists [18–19]. Considering cancer chemotherapy-induced or postoperative
93 nausea and vomiting, patients administered antineoplastic agents within 7 days or inherent anesthetics within 3 days prior
94 to receiving linezolid or vancomycin therapy were excluded [20–21]. We also excluded patients who were administered
95 linezolid or vancomycin for less than 3 days, were administered linezolid and vancomycin concomitantly, or had missing

data on birth date or prescribing date of linezolid or vancomycin. Antiemetics and concomitant medications were defined using ATC codes (Table 1S in the supplementary material).

Data collection

The following data were extracted from the JMDC claim database: sex, birth month, site of infection (respiratory, bloodstream, infectious endocarditis, skin and soft tissue, surgical site, intra-abdominal, musculoskeletal, and central nervous system), antibiotics (linezolid and vancomycin), antiemetics (metoclopramide, domperidone, and prochlorperazine), date of antibiotic and antiemetics prescription, diagnosis of chronic kidney disease (CKD), and hemodialysis. Drugs and diagnoses were identified using the ICD-10 and ATC codes, respectively (Table 1S–2S in the supplementary material). Hemodialysis was identified using medical procedure codes (C102, J038, and J042). The following criteria determined the duration of antimicrobial treatment: the date of the first prescription of linezolid or vancomycin was the earliest date recorded in the JMDC claims database. The end of the prescription date was defined as the day before the antimicrobial prescription was interrupted for more than four days, considering that patients undergoing hemodialysis were administered vancomycin three times a week on dialysis days.

Definitions and measurements

The primary endpoint was the occurrence of nausea and vomiting during linezolid or vancomycin treatment. The secondary endpoint was the analysis of risk factors for nausea and vomiting. We previously found that female sex is a risk factor for vomiting during linezolid therapy [7]. Therefore, to verify the effect of sex, we performed sub-analyses as a third

endpoint in the same manner as for the primary endpoint. In the sub-analyses, eligible patients were defined as (1) male and female cohorts and (2) linezolid and vancomycin cohorts. In the JMDC claims database, the ICD-10 code for nausea and vomiting is R11. However, because hospitals adopting the Diagnosis Procedure Combination system in Japan often do not register diseases with receipts other than the primary disease, the R11 code may not reflect the actual occurrence of nausea and vomiting. Therefore, in this study, we defined the occurrence of nausea and vomiting as the first prescription of antiemetics during linezolid or vancomycin therapy as a surrogate endpoint. Based on previous reports, metoclopramide, domperidone, and prochlorperazine, which are routinely prescribed in Japan, were selected as antiemetics [22]. As linezolid-induced nausea and vomiting are not widely recognized side effects, these antiemetic agents are not administered prophylactically.

Data analysis and sample size

All statistical analyses were performed using JMP® 16 software (SAS Institute Inc., Cary, NC, USA). Propensity score matching (PSM) was used to adjust for confounding factors from patient baseline characteristics between treatment groups, such as age, sex, kidney function and type of infection. Propensity scores were calculated using logistic regression analysis. We selected the following baseline covariates that may be associated with treatment decisions for the logistic regression model to estimate the propensity score: type of infection, age (years), sex, presence of CKD, and whether the patients underwent hemodialysis [23]. The c-index was calculated to validate the goodness of fit of the regression model for propensity score estimation. The calculated propensity scores were used to conduct 1:1 nearest-neighbor matching. The caliper value (caliper width) for nearest neighbor matching was set to 0.2 times the standard deviation of the logit of the

134 propensity scores (Supplementary Methods, Formula 1S). The standardized difference (d) was calculated to compare
135 patient baseline characteristics between the treatment groups before and after matching. The difference in patient baseline
136 characteristics between the treatment groups after matching was considered negligible if $d < 0.1$ (Supplementary Methods,
137 Formula 2S, 3S) [24].

138 To compare patient baseline characteristics, Pearson's chi-squared test or Fisher's exact test was performed for
139 dichotomous variables, and the Mann-Whitney U test for continuous variables. Logistic regression analysis was performed
140 to identify risk factors for nausea and vomiting. As the aforementioned covariates were used for propensity score estimation,
141 antimicrobial treatment and duration of administration were selected as covariates associated with nausea and vomiting.

142 Based on the results of our previous studies, the sample size was estimated based on the incidence of nausea and vomiting
143 (20% and 7%, respectively, in the linezolid and vancomycin groups) with a two-sided alpha value of 5% and a power of
144 80%, and set at 108 patients in each group (216 patients in total) [6, 7].

145 We performed sub-analysis (1) with PSM to adjust for confounding factors between the treatment groups. Sub-analysis
146 (2) was performed to compare the incidence of nausea and vomiting between female and male cohorts. Thus, PSM was not
147 used to adjust for sex differences because the propensity score is the probability of treatment assignment [23].

148

149 **Results**

150 Eligible patients (n = 1,215) who met the inclusion criteria were classified into the linezolid (n = 246) and vancomycin
151 groups (n = 969) (Fig. 1). A logistic regression model was used to calculate the propensity score, and the c-index was
152 calculated to be 0.62. After PSM, 241 patients were matched between the linezolid and vancomycin groups. The difference

153 in PSM-adjusted baseline characteristics between the two groups was d <0.1, except for the covariates of "administration
154 period" (Table 1). The administration period was significantly longer in the linezolid group. The proportion of nausea and
155 vomiting in the linezolid and vancomycin groups was 11.2% and 5.0%, respectively. The incidence of nausea and vomiting
156 was significantly higher in the linezolid group before and after PSM (p <0.05) (Fig. 2A and B). Logistic regression analysis
157 showed that linezolid administration was an independent risk factor for nausea and vomiting (odds ratio, 2.09; confidence
158 interval, 1.02–4.30) (Table 2).

159 In sub-analysis (1), the female and male cohorts comprised 363 and 852 eligible patients, respectively. After PSM, 71
160 and 170 patients were matched between the linezolid and vancomycin groups in the female and male cohorts, respectively
161 (Tables 3S, 4S in the supplementary material). The incidence of nausea and vomiting was higher in the linezolid group in
162 each cohort. However, there were no significant differences in the incidence of nausea and vomiting between the linezolid
163 and vancomycin groups in each cohort, and linezolid was not identified as a risk factor for nausea and vomiting (Fig. 1S
164 panels A to D, Tables 5S, 6S in the supplementary material).

165 In sub-analysis (2), the linezolid and vancomycin cohorts comprised 246 and 969 eligible patients, respectively. These
166 cohorts were classified into female (n = 71 and n= 292, respectively) and male (n = 175 and n= 677, respectively) (Tables
167 7S, 8S in the Supplementary Material). The incidence of nausea and vomiting was significantly higher in the female than
168 in the male groups (Fig. 2S, panel A in the Supplementary Material), and female sex was a risk factor for nausea and
169 vomiting in the linezolid cohort (Table 9S in the Supplementary Material). In contrast, no significant differences were
170 observed in the vancomycin cohort (Fig. 2S, panel B, Table 10S in Supplementary Material).

171

Discussion

Statement of key findings

The proportion of nausea and vomiting was higher in the linezolid group, and linezolid administration was an independent risk factor for nausea and vomiting. These results indicated that patients who received linezolid were more likely to be prescribed additional antiemetics. This result was consistent with that of our previous study reporting that linezolid administration might be associated with vomiting [6]. Therefore, the present study using the JMDC claims database could help externally validate our previous study.

We performed two sub-analyses to verify the effects of sex on nausea and vomiting. In sub-analysis (1), the higher incidence of nausea and vomiting in females was consistent with our previous report [7]. In sub-analysis (2), the incidence of nausea and vomiting was significantly higher in the female than in the male groups, and female sex was the risk factor for nausea and vomiting in the linezolid cohort. In contrast, no significant differences were observed in the vancomycin cohort. These results from the two sub-analyses suggest that linezolid should be administered with caution to female patients.

Strengths and Weaknesses

The use of the JMDC claims database for the present study provided the advantage of better generalizability than single-center studies. We could adjust the patient characteristics using PSM. Although the logistic regression model did not fit sufficiently in estimating the propensity score because the c-index was 0.62, the differences were considered negligible because the standardized difference in PSM-adjusted baseline characteristics was $d < 0.1$.

This study had several limitations. (1) This was a retrospective cohort study using the JMDC claims database, which did not include patients over the age of 75 years, laboratory and physical data, and treatment with over-the-counter medicine. It is possible that patients with renal impairment would be treated with vancomycin over linezolid, or patients with low body weight whose linezolid plasma concentration is increased would avoid linezolid treatment [25]. Therefore, unmeasured and unknown factors, including creatinine value and body weight, could be associated with antibiotic prescriptions. (2) It was unknown how long patients took the medications because there were no data on adherence. (3) Although the patients' baseline characteristics were adjusted using PSM, the result of the propensity score estimation did not fit well with the logistic regression model. In addition, there may be unmeasured covariates, which may reduce the precision of propensity score estimation. (4) Since antiemetics prescription was used as a surrogate indicator of nausea and vomiting, its relationship with the actual occurrence of nausea and vomiting is unknown. In general, the antiemetics used in this study are widely used for nausea and vomiting, but it is difficult to prove that they were used for the indicated disorders because Japanese claims data do not guarantee reliability for these disorders [26]. For example, prochlorperazine is approved for the treatment of schizophrenia and metoclopramide is sometimes used for hiccups. If the antiemetics were prescribed for these symptoms, then nausea and vomiting is overestimated in this study. However, by excluding patients undergoing cancer chemotherapy or surgery, we could exclude the effects of postoperative and chemotherapy-induced nausea and vomiting as much as possible. Therefore, nausea and vomiting in this study are most likely underestimated. (5) In the sub-analyses, stratification according to sex or antibiotic treatment resulted in a smaller sample size and lower statistical power because the sample size was determined according to the primary endpoint. However, the incidence of nausea and vomiting in the linezolid group was lower than that in the vancomycin group, which was consistent with the

primary endpoint analysis.

Interpretation

Possible mechanisms of linezolid-induced nausea and vomiting include the emetogenicity of linezolid, serotonergic interactions [20], symptoms of lactic acidosis [27], and symptoms of hyponatremia due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [28]. Lactic acidosis and SIADH are rare side effects, and lactic acidosis has been associated with long-term linezolid administration [29].

The treatment duration was significantly longer in the linezolid group ($d \geq 0.1$) because it was not adjusted by PSM. This result indicates that the observation period was longer in the linezolid group, which indicates a greater change in the development of side effects. Although the duration of treatment was evaluated as a covariate in the logistic regression analysis, linezolid therapy was an independent risk factor for nausea and vomiting. Furthermore, long-term linezolid administration is associated with lactic acidosis [29], which may indicate similar results to previous studies. Linezolid is often changed from injectable to oral administration based on patients' condition. This change might be a factor in the long duration of linezolid therapy.

In the present study, we did not compare the incidence of nausea and vomiting between oral and injectable forms because we aimed to determine whether linezolid therapy was more associated with nausea and vomiting than vancomycin therapy. Our previous study identified risk factors for vomiting in patients receiving linezolid therapy, and there was no significant association between the linezolid form and vomiting [7].

Further research

Further studies are required to investigate the mechanisms for nausea and vomiting associated with linezolid administration, and clarify the association between sex and nausea and vomiting during linezolid therapy.

Conclusion

In the present study, we examined the causal relationship between linezolid and nausea and vomiting in a Japanese claims database collected from multiple health insurance associations and verified the association in a wide range of patient populations, as in previous single-center studies. The risk of nausea and vomiting was higher with linezolid than with vancomycin. Linezolid should be administered with caution, especially in women. Nausea and vomiting not only severely impair patients' quality of life, but also cause disadvantages such as interruption of treatment. However, effective agents for nausea and vomiting during linezolid therapy are unknown. Therefore, elucidation of the mechanism of linezolid-induced nausea and vomiting, which remains unknown, is a future challenge.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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318 **Figures**

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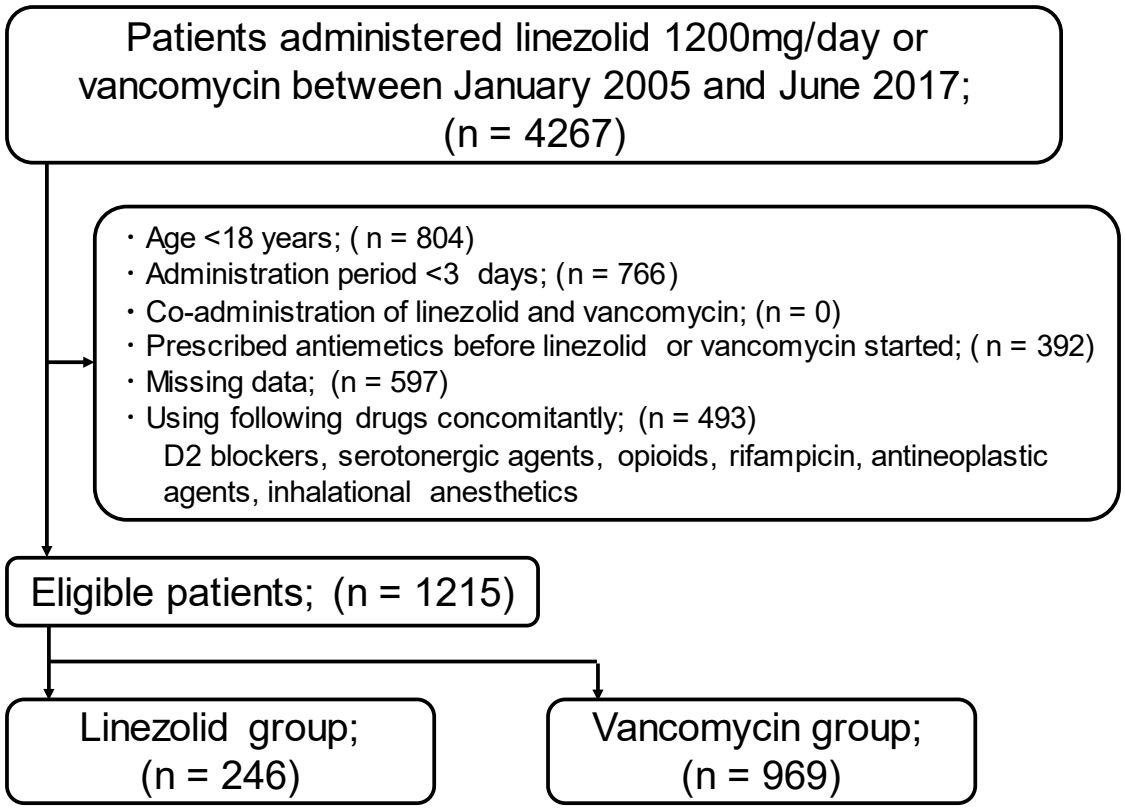

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321 **Fig. 1** Flowchart of study patient selection

322 D2 blockers, dopamine type 2 blockers.

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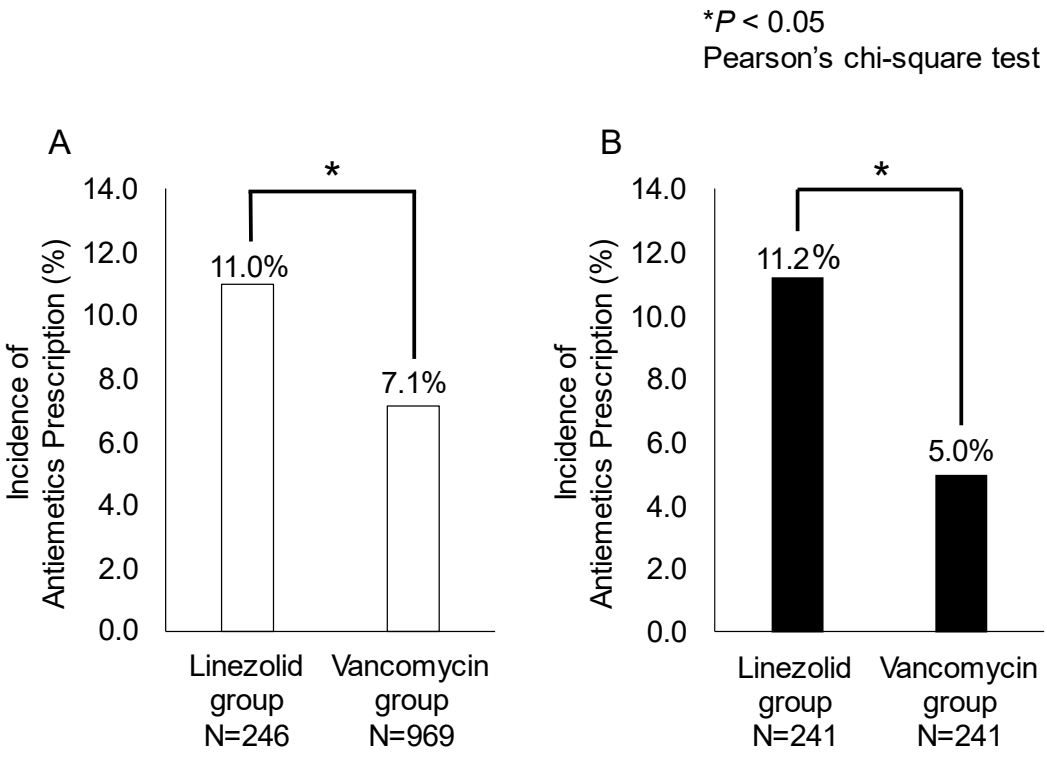

Fig. 2 Proportion of antiemetics prescription (A) before and (B) after propensity score matching

Tables

Table 1 Comparison of characteristics of patients before and after propensity score matching

	Before PSM						After PSM					
	Linezolid group N=246		Vancomycin group N=969		*P* value	Std diff	Linezolid group N=241		Vancomycin group N=241		*P* value	Std diff
Sex (female), n (%)	71	28.9	292	30.1	0.697	0.028	71	29.5	64	26.6	0.687	0.065
Age (year), median (range)	52	18–75	54	18–74	0.144	0.097	52	18–75	53	19–74	0.741	0.014
Age (year) ≥65, n (%)	34	13.8	177	18.3	0.100	0.121	34	14.1	40	16.6	0.448	0.069
Administration period (days), median (range)	9	3–91	7	3–71	<0.001*	0.362	9	3–91	7	3–52	0.001*	0.247
Chronic renal disease, n (%)	25	10.2	125	12.9	0.244	0.086	25	10.4	22	9.1	0.645	0.042
Hemodialysis, n (%)	35	14.2	124	12.8	0.552	0.042	35	14.5	35	14.5	1.000	<0.001
Pneumonia, n (%)	50	20.3	194	20.0	0.915	0.008	50	20.7	48	19.9	0.821	0.021
Blood stream infection, n (%)	50	20.3	252	26.0	0.066	0.135	50	20.7	50	20.7	1.000	<0.001
Endocarditis, n (%)	4	1.6	30	3.1	0.212	0.097	4	1.7	3	1.2	1.000	0.035
Skin and soft tissue infection, n (%)	14	5.7	52	5.4	0.841	0.014	14	5.8	10	4.1	0.402	0.076
Surgical site infection, n (%)	22	8.9	55	5.7	0.060	0.126	22	9.1	19	7.9	0.624	0.045
Intra-abdominal infection, n (%)	14	5.7	31	3.2	0.065	0.121	14	5.8	16	6.6	0.706	0.034
Bone, joint and musculoskeletal infection, n (%)	25	10.2	36	3.7	<0.001*	0.256	20	8.3	18	7.5	0.735	0.031
Central nerve system infection, n (%)	12	4. 9	89	9.2	0.029*	0.169	12	5.0	12	5.0	1.000	<0.001
Urinary tract infection, n (%)	11	4.5	36	3.7	0.583	0.038	11	4.6	15	6.2	0.420	0.074

PSM, propensity score matching; Std diff, Standardized difference.

Differences in patients' characteristics before and after PSM were considered ignorable if the Std diff was <0.1.

*P values <0.05 were considered statistically significant.

333 Table 2 Multivariate analysis of risk factors of nausea and vomiting during linezolid or vancomycin therapy

	OR	95% CI	*P* value
Linezolid administration	2.09	1.018–4.299	0.045*
Administration period (days)	1.03	1.008–1.060	0.008*

334 OR, odds ratio; CI, confidence interval.

335 **P* values <0.05 were considered statistically significant.

336 Odds ratio of administration period indicates odds per single unit increase.

337