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1 Title

2 Investigation of the Risk Factors of Vomiting during Linezolid Therapy: A Retrospective Observational Study

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13 Key Words: linezolid, nausea and vomiting, adverse drug effects, hyponatremia

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18 Abstract

19 **Purpose** Some clinical studies have reported the occurrence of nausea and vomiting with linezolid (LZD) administration. However, no studies have evaluated nausea and vomiting as primary endpoints. In a previous study, we noted a possible relationship between LZD and vomiting, but risk factors were not identified. Therefore, the aim of the present study was to identify them.

23 **Methods** Patients who received LZD 600 mg twice daily at Hokkaido University Hospital from September 2008 to April 2019 were enrolled in this retrospective observational study. Patient characteristics, concomitant medications, laboratory data, and the occurrence of vomiting were obtained from electronic medical records. Logistic regression analysis was performed to identify risk factors for vomiting, including age, sex, body weight, concomitant medications, and surgeries.

27 **Results** A total of 496 patients were included in this study, of which 90 experienced vomiting. By multivariate logistic regression analysis, female sex (adjusted odds ratio [aOR], 2.69; 95% confidence interval [CI], 1.62–4.47), ≥ 10 days of LZD administration (aOR, 2.57; CI, 1.46–4.50), and hyponatremia (aOR, 2.96; CI, 1.72–5.10) were identified as independent risk factors for vomiting; administration of serotonergic agents (aOR, 0.23; CI, 0.07–0.82) was negatively associated.

31 **Conclusions** This study is the first to successfully identify risk factors for LZD-induced vomiting. Careful monitoring of patients with these risk factors may lead to safer and sustainable LZD administration.

34 Introduction

35 Linezolid (LZD) is an antimicrobial agent used against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci. It is widely used to treat bacteraemia, pneumonia, and skin and soft tissue infections [1–2]. It has also been used to treat bone and joint infections [1] because it penetrates bone and joints well [3]. Previously, we observed multiple cases of nausea and vomiting, during LZD treatment for bone and joint infections. In a meta-analysis of phase III studies of LZD [4], the incidence of LZD-related vomiting was 1.1%. Another phase III study that compared the efficacy of LZD with tedizolid reported a nausea incidence of 12.2% and vomiting incidence 5.6% in patients receiving LZD [5]. The other meta-analysis focused on the efficacy and safety of LZD relative to other antibiotics and reported a nausea risk ratio of 1.58 (95% confidence interval [CI]: 0.91–2.74) and a vomiting risk ratio of 1.70 (95% CI: 1.02–2.82) [6]. In these studies, the LZD dose was 1,200 mg daily administered for approximately 10 days [4–6]. The incidence of LZD-related gastrointestinal adverse reactions, including nausea and vomiting, was 48.5%, occurring between 2 and 4 weeks of LZD treatment for drug-

45 resistant tuberculosis (XDR-TB) infection; the dose was 1,200 mg daily during the first 4–6 weeks and then 300–600 mg
46 daily as tolerated, administered for 2–24 months [7]. Therefore, nausea and vomiting may be more common with LZD than
47 with other antibiotics. However, these reports on nausea and vomiting were evaluated as part of the efficacy and safety of
48 linezolid. To date, only our previous study has evaluated the incidence and/or risk factors for LZD-induced nausea and
49 vomiting as the primary endpoint [8]. Although dose adjustments are not needed for renal function or body weight, plasma
50 LZD concentration has been reported to increase in patients with renal impairment and those who are underweight, leading
51 to thrombocytopenia [9–10]. In addition, LZD interacts with selective serotonin reuptake inhibitors (SSRIs) due to its non-
52 selective monoamine oxidase (MAO) inhibitory activity [11], which may cause serotonin (5-hydroxytryptamine; 5-HT)
53 syndrome [12].

54 In clinical settings, given patient variations and concomitant medications, it is possible that alterations in LZD
55 pharmacokinetics and/or drug-drug interactions may induce nausea and vomiting. In a previous study, we reported that
56 patients receiving LZD had a significantly higher incidence of vomiting than patients treated with other antibiotics; however,
57 we could not investigate the risk factors for LZD-induced vomiting because of the insufficient number of patients enrolled
58 [8]. Therefore, this study aimed to identify the risk factors associated with LZD-induced vomiting.

59

60 **Materials and Methods**

61 **Study design**

62 A single-centre, retrospective, observational study was conducted.

63

64 **Population and sample size**

65 The inclusion criterion for this study was treatment with LZD, 600 mg twice daily, orally or intravenously for the first
66 time at Hokkaido University Hospital from September 2008 to April 2019. The exclusion criteria were: age <18 years, <3
67 days of administration, at least one vomiting episode within 1 week before the start of LZD administration, and missing data.
68 Patients who met the criteria were divided into vomiting and non-vomiting groups. The intended sample size was 500 cases
69 for the logistic regression analysis. In this regression model, it has been reported that when events per variate (EPV) ≥ 10 ,
70 there were no major problems with the accuracy and precision of the results, but when EPV <10, the bias of the regression
71 coefficients increased and often led to extreme values of the maximum likelihood estimates [13]. Thus, our calculated sample
72 size was needed to incorporate 10 independent variables if the incidence of vomiting was assumed to be 20%, based on a
73 previous study [8].

74

75 **Data collection**

76 The following information was extracted from medical records retrospectively: occurrence of vomiting, sex, age, body
77 weight, serum creatinine level, baseline and minimum serum sodium level (S-Na) during the administration period,
78 administration period of LZD, administration route, concomitant medications, surgery under general anaesthesia, and cancer
79 chemotherapy. Dopamine type2 (D2) receptor blockers, serotonergic agents, opioid analgesics, tramadol, and rifampicin
80 (RFP) were extracted as concomitant medications. Creatinine clearance (Ccr) was calculated using the Cockcroft-Gault
81 formula [14]. Onset of vomiting was defined as the reflux of gastric contents from the mouth. Information about S-Na was
82 extracted because antidiuretic hormone inappropriate secretion syndrome, which is a rare side effect of LZD, may occur,
83 and nausea is a symptom of hyponatremia [15].

84 With regard to concomitant drugs, treatment with tramadol and other opioids was extracted separately because tramadol
85 is a weak MAO inhibitor and its interaction with LZD was considered. To investigate whether D2 receptor blockers
86 contribute to the suppression of vomiting, patients were scored for treatment with D2 receptor blockers at the start of LZD
87 administration. Serotonergic agents were defined as drugs that stimulate or enhance the effects of 5-HT receptors and did
88 not include antagonists. Since RFP interacts with LZD [16], it was also evaluated.

89 Considering postoperative nausea and vomiting (PONV) [17], patients who received LZD within 3 days after surgery under
90 general anaesthesia were defined as “patients with operation.” Similarly, considering the incidence of chemotherapy-induced
91 nausea and vomiting (CINV) [18], patients who received LZD within 7 days after cancer chemotherapy were defined as
92 “patients with cancer chemotherapy.”

93 94 **Definitions and measurements**

95 The primary endpoint was the identification of risk factors for vomiting associated with LZD administration. Time from the
96 start of LZD administration to the onset of vomiting was also evaluated. Risk factors for vomiting were defined separately as
97 direct or potential. Direct factors that may be directly related to vomiting were: hyponatremia ($S\text{-Na} \leq 134$ mEq/L) [19], use of
98 concomitant drugs (D2 receptor blockers, serotonergic agents, opioid analgesics, tramadol, RFP), operation, and cancer
99 chemotherapy. The potential risk factors were: elderly (≥ 65 years of age), female sex, low body weight (< 40 kg), route of
100 administration (intravenous infusion), duration of administration (≥ 10 days), renal impairment ($\text{Cr} < 60$ mL/min), and renal
101 replacement therapy. Female sex was evaluated because this factor has been reported as a risk factor for nausea and vomiting
102 in PONV and CINV [17–18]. Since low body weight and renal impairment generally increase LZD concentration, they have
103 also been evaluated as risk factors [9–10]. The cut-off value for the administration period was determined using an ROC curve.
104 Hyponatremia was defined as $S\text{-Na} > 134$ mEq/L and ≤ 134 mEq/L before the start of and after LZD administration, respectively
105 [19]. Because there are several reports on LZD-induced hyponatremia [20–21], we examined the incidence of vomiting in
106 patients with or without hyponatremia to evaluate its contribution. Hyponatremia was stratified according to the Common
107 Terminology Criteria for Adverse Events v5.0 [22] because it was necessary to distinguish between patients whose
108 hyponatremia developed before and after LZD administration.

109 110 **Data analysis**

111 Statistical analyses were performed using JMP® 14 (SAS Institute Inc., Cary, NC, USA). To compare patient characteristics,
112 the Mann-Whitney U test was performed for continuous variables, with Pearson’s chi-squared test or Fisher’s exact test
113 performed for categorical variables. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) using logistic regression
114 analysis were evaluated to identify risk factors. Statistical significance was set at $P < 0.05$. Direct risk factors were inevitably
115 incorporated into multivariate analysis: hyponatremia, concomitant use of dopamine D2 blockers, serotonergic agents, opioids,
116 tramadol, RFP, operations, and cancer chemotherapy. For other potential risk factors (elderly, sex, low body weight, route of
117 administration, duration of administration, renal impairment, and renal replacement therapy), we performed multivariate
118 analysis for only those that were $P < 0.2$ in univariate analysis.

119 120 **Results**

121 **Patient characteristics**

122 LZD was administered to 724 patients, of whom 496 satisfied the inclusion criteria (Fig. 1). Ninety patients who developed
123 vomiting were allocated to the vomiting group, with the remaining 406 in the non-vomiting group. The incidence of vomiting
124 was 18.1%. The median time from the start of LZD administration to the first onset of vomiting was 6 days (range 1–33).
125 Significant differences between the vomiting and non-vomiting groups were observed for female sex (44.4% vs. 33.5%), body
126 weight [median, 55.4 kg (range 35.9–110.0) vs. 60.0 kg (range 32.4–118.1)], administration period [median 14 days (range 4–
127 64) vs. 10 days (range 4–41)], S-Na at baseline [median 138 mEq/L (range 128–151) vs. 139 mEq/L (range 116–182)],
128 minimum S-Na during the administration period [median, 133.5 mEq/L (range 116–146) vs. 136 mEq/L (range 116–172)],
129 hyponatremia (40.0% vs. 17.2%) including each grade classification, and concomitant use of RFP (14.4% vs. 6.4%) (Table 1).

131 **Logistic regression analysis**

132 Female sex, administration period, and renal impairment were $P < 0.2$ in univariate analysis and therefore incorporated
133 into the multivariate analysis with direct risk factors. In the multivariate logistic regression analysis, female sex (aOR, 2.69;
134 95% CI, 1.62–4.47), administration period (≥ 10 days) (aOR, 2.57; CI, 1.46–4.50), hyponatremia (aOR, 2.96; CI, 1.72–5.10),
135 and concomitant use of serotonergic agents (aOR, 0.23; CI, 0.07–0.82) were identified as risk factors for vomiting (Table 2).

136

137 **Vomiting in patients with or without hyponatremia**

138 The incidence of vomiting in patients with hyponatremia was approximately twice as high as that in patients without
139 hyponatremia (26.7% vs. 12.2%). In particular, the incidence of vomiting was higher in patients with hyponatremia that
140 developed during LZD administration than in those exhibiting hyponatremia before administration (34.0% vs. 18.8%) (Table
141 3).

142

143 **Discussion**

144 Vomiting is induced by multiple medical treatments and represents a significant reduction in a patient's quality of life. We
145 reported that vomiting is associated with LZD administration in previous study [8]; therefore, we examined the risk factors
146 for LZD-induced vomiting.

147 The overall incidence of vomiting was 18.1%, similar to that reported in a previous study (23.4%) [8]. The median time
148 from the start of LZD administration to vomiting was consistent with previous reports [4–7]. Multiple logistic regression
149 revealed that female sex, administration period (> 10 days), and hyponatremia were independent risk factors for vomiting
150 associated with LZD. In contrast, the concomitant use of serotonergic agents was an independent suppression factor for
151 vomiting. Although renal impairment and being underweight are risk factors for thrombocytopenia [9–10], we found that
152 LZD-induced vomiting was not associated with either of them.

153 The incidence of vomiting group was higher in women and was determined to be an independent risk factor. The
154 mechanism of nausea and vomiting, especially CINV, is thought to involve multiple signalling pathways, including the D2,
155 5-HT₃, and neurokinin 1 receptors [18]. D2 receptor sensitivity and expression were affected by oestradiol in female rats
156 [23–24]. In addition, droperidol, a D2 receptor blocker, significantly prevented PONV in women in a randomised controlled
157 trial (RCT) that included $> 5,000$ patients [25]. These reports suggest a sex-associated difference in D2 receptor sensitivity.
158 In contrast, the same RCT also reported that the menstrual cycle affects oestradiol concentration, but not the incidence of
159 PONV [25]. Although the relationship between nausea and vomiting and sex is still controversial, female sex has been
160 previously reported as a risk factor for PONV [17] and CINV [18].

161 The administration period (≥ 10 days) was significantly longer in the vomiting group. Lactic acidosis (LA) is an infrequent
162 side effect of LZD; its primary symptoms include nausea and vomiting. A relationship between LA and LZD has been
163 reported in several studies. The U.S. Food and Drug Administration (FDA) label information of Zyvox[®] states that LA is
164 more likely when administered for more than 28 days [26]. In a recent study, LZD-induced LA occurred at 35 ± 29 days
165 (mean \pm standard deviation); its mechanism is hypothesised to include the inhibition of protein synthesis and aerobic
166 respiration via mitochondrial ribosome malfunction [27]. Another study using the FDA Adverse Event Reporting System
167 showed that numbers of reports regarding LA increased when LZD administration period exceeded 2 weeks [28]. These
168 reports also support the hypothesis that LZD-induced vomiting is related to LA. However, the cut-off value for administration
169 period in this study was defined as 10 days using the receiver operating characteristic (ROC) curve, which is shorter than
170 the previous report [27–28], in which 20 patients received LZD for over 28 days. We were unable to assess the occurrence
171 of LA in this study because very few patients underwent blood-gas analysis. Additional research is needed to determine the
172 prevalence and mechanisms of LZD-induced LA.

173 Although there were no significant differences in the baseline incidence of hyponatremia between the two groups, the
174 incidence increased in the vomiting group after LZD administration. Moreover, the severity of hyponatremia was higher in

175 the vomiting group (Table 1) and was more common in patients with hyponatremia after LZD administration (Table 3).

176 Hyponatremia has been identified as a risk factor for vomiting (Table 2). Its incidence was 18.1% in this study, which is
177 similar to that in recent reports [20–21]. Considering the increased incidence and the high severity of hyponatremia in the
178 vomiting group, it is possible that vomiting might be a symptom of hyponatremia that developed during LZD administration.
179 However, vomiting is common even in patients without hyponatremia (Table 3); therefore, it cannot be explained by
180 hyponatremia alone. It is also possible that hyponatremia developed as a consequence of vomiting rather than vomiting due to
181 hyponatremia. However, we were unable to verify the temporal relationship between vomiting and hyponatremia because blood
182 tests were not performed before the onset of vomiting in all cases; most patients underwent blood tests performed at least two
183 days before or after the day they vomited. Therefore, we could only infer a relationship between vomiting and sodium levels
184 by observing the lowest sodium levels. Thus, further studies are required to elucidate the association between vomiting and
185 hyponatremia.

186 The concomitant use of serotonergic agents was negatively correlated vomiting; other medications did not affect vomiting
187 (Table 2). First, we hypothesised that concomitant use of serotonergic agents, such as SSRIs, with LZD could induce vomiting
188 via an augmented release of 5-HT and stimulation of 5-HT receptors, but the opposite effect was observed. In this study,
189 trazodone and SSRIs were the most commonly used serotonergic agents in 21 and 20 cases, respectively (duplicated cases
190 existed). Trazodone usage also includes single-dose administration, as for hypnotics; however, it was unclear whether trazodone
191 was regularly administered. In addition to its SSRI-like effect, trazodone also inhibits 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptors
192 [29]. In particular, inhibition of 5-HT_{2C} receptors contributes to a CINV prophylactic effect, similar to that of olanzapine [30].
193 Considering these effects, it is possible that trazodone has an antiemetic effect similar to that of olanzapine. SSRIs have been
194 reported to desensitise 5-HT receptors such as 5-HT_{2C} and 5-HT₃ [31]. This may contribute to a reduction in the incidence of
195 vomiting associated with LZD. In this study, drugs that increase 5-HT secretion were defined as serotonergic agents, but several
196 of these have multiple 5-HT receptor antagonistic mechanisms, such as mirtazapine [32]. Considering these mechanisms, it is
197 possible that serotonergic agents may have an antiemetic effect via desensitisation or blocking of various 5-HT receptors.

198 We observed no difference in the proportions of patients who concomitantly used D₂ receptor blockers at baseline between
199 the two groups; so it is possible that LZD-induced vomiting was not suppressed by D₂ receptor blockers. RFP was not detected
200 as a risk or suppression factor. Since RFP decreases the LZD blood concentration, LZD concentration may not be related to the
201 occurrence of LZD-induced vomiting [16]. This hypothesis is also supported by our finding that “renal impairment (Ccr <60
202 mL/min) and low body weight (<40 kg)”, which are factors that generally increase the blood LZD concentration, were not
203 associated with LZD-induced vomiting [9–10].

204 This study has several limitations. First, it was a single-centre retrospective observational study. Second, the patients were
205 not followed up after discontinuation of LZD. It is necessary to determine if the patients experienced nausea or any
206 improvement in vomiting. However, as nausea is a subjective symptom it is difficult to evaluate its presence, absence, and
207 severity from electronic medical records. Third, our study did not reach EPV ≥ 10 , that is, the number of cases enrolled was
208 496 and the number of factors applied in multivariate analysis was 11. Thus, the accuracy and precision of logistic regression
209 may decrease [13]. It is necessary to perform an additional study by increasing the number of subjects. Fourth, other causes of
210 vomiting, such as comorbidities and concomitant medications, could not be completely excluded. Drugs administered as a
211 single dose, such as anti-emetics, are also defined as concomitant medications; however, it was not clear whether a single dose
212 was regularly administered. Therefore, to exclude confounding effects, our evaluations excluded the concomitant use of 5-HT
213 agonists, opioids, tramadol, and RFP. The incidence of vomiting was 17.0% (56 of 328 cases), which was almost the same as
214 the overall incidence of vomiting. This result supports the hypothesis that LZD administration induces vomiting.

215 We succeeded in identifying risk factors for LZD-induced vomiting for the first time, including female sex, long-term
216 administration, and the development of hyponatremia. Among them, long-term administration may be associated with LA and
217 may be life-threatening. However, the causes of vomiting often cannot be identified because multiple factors coexist, and it
218 must be considered that there are many cases in which LZD administration was discontinued due to lack of tolerance. Recently,

219 some studies have reported that the incidence of hyponatremia in patients receiving LZD is approximately 20% [20–21].
220 This is consistent with the results of the present study. Since hyponatremia is known to cause vomiting, it may exist as a
221 background factor during LZD administration. Because vomiting occurs as a result of complex biological reactions, causes
222 related to LZD are not limited to the risk factors identified in this study. Improved management of these side effects is
223 expected to support safer and more sustainable LZD treatment.

224

225 **Declarations**

226 **Authors' Contribution**

227 Study concept and design: Takezo Tsutsumi, Shungo Imai, and Yoh Takekuma; acquisition of data: Takezo Tsutsumi;
228 analysis and interpretation of data: all authors; drafting the manuscript: Takezo Tsutsumi; revising the manuscript critically
229 for important intellectual content: All authors. All the authors approved the version of the manuscript.

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232 **Conflicts of interest/Competing interests**

233 The authors declare no conflicts of interest.

234 **Availability of data and material**

235 The datasets generated during and analysed during the current study are available from the corresponding author upon
236 reasonable request.

237 **Code availability**

238 Not applicable.

239 **Ethics approval**

240 This study was approved by the Institutional Review Board of the Hokkaido University Hospital for Clinical Research
241 (study protocol NO. 019-0213).

242 **Consent to participate**

243 Not applicable.

244 **Consent for publication**

245 Not applicable

246

247

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335

336 TABLES

337 **Table 1** Comparison of the characteristics between patients with vomiting and without vomiting

	Vomit (n = 90)	Non-Vomit (n = 406)	P value
Age (year), median (range)	61.5 (20–89)	62 (20–89)	0.98
Age (year), ≥65, n (%)	37 (41.1)	175 (43.1)	0.73
Sex (female), n (%)	50 (44.4)	135 (33.5)	<0.01*
Body weight (kg), median (range)	55.4 (35.9–110.0)	60.0 (32.4–118.1)	0.02*
Body weight (kg) <40, n (%)	6 (6.67)	19 (4.68)	0.43
Administration period of LZD (days), median (range)	14 (4–64)	10 (4–41)	<0.01*
Intravenous infusion of LZD, n (%)	56 (62.2)	238 (58.6)	0.53
Baseline S-Na (mEq/L), median (range)	138 (128–151)	139 (116–182)	0.03*
Minimum S-Na (mEq/L), median (range)	133.5 (116–146)	136 (116–172)	<0.01*
Baseline S-Na ≤134 mEq/L, n (%)	18 (20.0)	78 (19.2)	0.88
With hyponatremia (S-Na ≤134 mEq/L), n (%) ^a	36 (40.0)	70 (17.2)	<0.01*
Grade1 (134 ≥ S-Na ≥130 mEq/L), n (%)	21 (23.3)	56 (13.8)	0.02*
Grade2 (130 > S-Na ≥125 mEq/L), n (%)	8 (8.9)	12 (3.0)	0.02*
Grade3 (125 > S-Na ≥120 mEq/L), n (%)	4 (4.4)	2 (0.5)	0.01*
Grade4 (S-Na <120 mEq/L), n (%)	3 (3.3)	0 (0)	<0.01*
Serum creatinine (mg/dL), median (range)	0.89 (0.19–9.5)	0.82 (0.2–12.5)	0.90
Creatinine clearance (mL/min), median (range)	62.3 (5.6–369.8)	69.1 (4.0–438.3)	0.19
With renal impairment (Ccr <60 mL/min), n (%)	44 (48.9)	167 (41.1)	0.18
Concomitant baseline use of dopamine D2 blockers, n (%)	11 (12.2)	75 (18.5)	0.17
Concomitant use of serotonergic agents, n (%)	3 (3.3)	38 (9.4)	0.09
Concomitant use of opioids, n (%)	21 (23.3)	78 (19.2)	0.38
Concomitant use of tramadol, n (%)	11 (12.2)	49 (12.1)	1.00
Concomitant use of RFP, n (%)	13 (14.4)	26 (6.4)	0.02*
With operations, n (%)	21 (23.3)	64 (15.8)	0.08
With chemotherapy, n (%)	5 (5.6)	23 (5.7)	1.00

338 LZD, linezolid; S-Na, serum sodium level; Ccr, creatinine clearance; RFP, rifampicin

339 *Statistical significance was set at $p < 0.05$.340 ^aHyponatremia was defined as baseline S-Na >134 mEq/L and reduced to ≤134 mEq/L after LZD administration.

341

342 **Table 2** Univariate and multivariate analysis for risk factors of LZD-induced vomiting

	Univariate			Multivariate		
	OR	95% CI	<i>P</i> value	aOR	95% CI	<i>P</i> value
Age (year) ≥ 65 , n (%)	0.92	0.58–1.46	0.73			
Sex (female), n (%)	2.51	1.58–4.01	<0.01 [†]	2.69	1.62–4.47	<0.01*
Body weight (kg) <40, n (%)	1.45	0.56–3.75	0.44			
Intravenous infusion of LZD, n (%)	1.16	0.73–1.86	0.53			
Administration period of LZD (days) ≥ 10 , n (%)	2.89	1.71–4.89	<0.01 [†]	2.57	1.46–4.50	<0.01*
With hyponatremia (S-Na ≤ 134 mEq/L), n (%) ^a	3.20	1.95–5.24	<0.01 [†]	2.96	1.72–5.10	<0.01*
With renal impairment (Ccr <60 mL/min), n (%)	1.37	0.87–2.16	0.18 [†]	1.25	0.75–2.06	0.39
Renal replacement therapy, n (%)	1.284	0.61–2.70	0.507			
Concomitant baseline use of dopamine D2 blockers, n (%)	0.61	0.31–1.21	0.16 [†]	0.71	0.34–1.47	0.36
Concomitant use of serotonergic agents, n (%)	0.33	0.10–1.11	0.07 [†]	0.23	0.07–0.82	0.02*
Concomitant use of opioids, n (%)	1.28	0.74–2.21	0.38	1.27	0.70–2.30	0.44
Concomitant use of tramadol, n (%)	1.01	0.50–2.04	0.97	0.86	0.39–1.86	0.69
Concomitant use of RFP, n (%)	2.47	1.21–5.02	0.01 [†]	2.02	0.88–4.63	0.11
With operations, n (%)	1.63	0.93–2.84	0.09 [†]	1.25	0.65–2.39	0.50
With chemotherapy, n (%)	0.98	0.36–2.65	0.97	1.16	0.40–3.40	0.79

343 LZD, linezolid; S-Na, serum sodium level; Ccr, creatinine clearance; RFP, rifampicin; OR, odds ratio; aOR, adjusted odds
 344 ratio; CI, confidence interval.

345 [†] These variables were incorporated into the multivariate analysis.

346 * Statistical significance was set at $P < 0.05$.

347 ^a Hyponatremia was defined as baseline S-Na >134 mEq/L and reduced to ≤ 134 mEq/L after LZD administration.

348

349 **Table 3** Incidence of vomiting in patients with hyponatremia

	Incidence of vomiting, n (%)
All hyponatremia patients in this study (n = 202)	54 (26.7)
With hyponatremia before LZD administration (n = 96)	18 (18.8)
With hyponatremia during LZD administration (n = 106)	36 (34.0)
No hyponatremia episode (n = 294)	36 (12.2)

350 LZD, linezolid

351

352

353 **FIGURE LEGENDS**

354

355 **Fig. 1** Flowchart of patients included in this study

Patients administered linezolid at the
Hokkaido University Hospital
September 2008 to April 2019;
(n = 724)

- Age <18 years; (n = 83)
- Administration period <3 days; (n = 89)
- Vomiting exist before LZD started; (n = 47)
- Missing data; (n = 9)

Study patients; (n = 496)

Vomiting group;
(n = 90)

Non vomiting group;
(n = 406)