Incidence and Risk Factors of Hypokalemia in Tazobactam/Piperacillin-administered Patients

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Tazobactam/piperacillin (TAZ/PIPC) is a useful antimicrobial agent with broad antibacterial activity. Hypokalemia is considered a rare side effect of TAZ/PIPC; however, it may occur more often than previously thought. In this study, hypokalemia frequency and risk factors were examined in 420 patients treated with TAZ/PIPC. Our results demonstrated that the hypokalemia incidence was 24.8% (grade 1–2: 18.3%, grade 3–4: 6.4%). In addition, multivariate analysis revealed that age [odds ratio 1.057, 95% confidence interval 1.024–1.090, cutoff value 80.5 years] is a risk factor. Although the “Daily dosage/creatinine clearance” was not significant in multivariate analysis, univariate analysis indicated it be to be significant, with a cutoff value of 294.9 mg/mL/min. Furthermore, a “body mass index of 19.7 kg/m² or higher”, “serum potassium level before administration of 3.95 mEq/L or more”, and “no empirical treatment for administration purposes” appeared to prevent the hypokalemia development. Overall, the hypokalemia incidence rate in TAZ/PIPC-administered patients was as high as 20%, with patients aged > 80.5 years considered a high-risk group. Thus, careful monitoring of potassium levels in patients treated with TAZ/PIPC, particularly those aged > 81 years, is warranted.

Key words—tazobactam/piperacillin; hypokalemia; risk factor; incidence; age; body mass index

INTRODUCTION

Hypokalemia is a relatively common electrolyte anomaly with mild cases seen in approximately 21% of inpatients and 2–3% of outpatients.^{1,2)} Severe cases of hypokalemia can lead to respiratory muscle/quadruplegia paralysis and paralytic ileus, with the appearance of characteristic U waves in the electrocardiogram and the flattening of T wave hyperexcitability of the heart, including ventricular premature contraction.³⁾

Tazobactam/piperacillin (TAZ/PIPC) is an injectable antibiotic that is prepared by combining tazobactam, a β -lactamase inhibitor, and piperacillin, a penicillin-based drug with broad spectrum antimicrobial activity, at a potency ratio of TAZ : PIPC 1 : 8.⁴⁾ Accordingly, TAZ/PIPC is considered to have broad antibacterial activity against Gram-positive bacteria, Gram-negative bacteria, including *Pseudomonas aeruginosa*, and anaerobic bacteria. It is recommended as a first-line drug in major medical practice guidelines for treating infectious diseases worldwide. In Japan, TAZ/PIPC was approved in 2015 for febrile neutropenia (FN). Additionally, TAZ/PIPC is an important treatment for a variety of infectious diseases, including pneumonia, pye-

lonephritis, peritonitis, septicemia, and cholangitis,⁵⁾ however, TAZ/PIPC may cause side effects, including chloride reduction and hypokalemia. The incidence rates of potassium reduction and hypokalemia associated with TAZ/PIPC during clinical trials for general infectious diseases is reported to be 3.3% (2.7% in mild cases and 0.6% in moderate cases), with a clinical trial of patients with FN reporting 6.0% (0.9% for grade 2, 4.3% for grade 3, and 0.9% for grade 4).⁴⁾ In contrast, no reports exist of hypokalemia as a side effect of PIPC alone.⁶⁾ Moreover, except for diarrhea, there were no significant differences in the side effects of PIPC as a single agent and TAZ/PIPC.⁷⁾ However, in patients entering the intensive care unit, PIPC reportedly causes electrolyte abnormalities, such as potassium and magnesium, although the serum creatinine levels are within reference values.⁸⁾ From 2008 to 2018, nine cases have been reported in the Pharmaceuticals and Medical Devices Agency (PMDA)’s “Information on cases report that side effects are suspected”.⁹⁾ We have also often encountered cases where antimicrobial drugs must be changed due to hypokalemia caused by TAZ/PIPC administration. Several reports of hypokalemia caused by TAZ/PIPC have also been found,^{7,10,11)} but there are very few studies investigating the underlying factors of this side effect. However, since hypokalemia is a poor prognostic factor for heart

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failure patients, and it represents an additional risk of developing stroke,^{12,13)} it is important to understand the hypokalemia onset rate and associated risk factors in actual clinics.

Therefore, in this study, a retrospective analysis was performed to clarify the incidence of hypokalemia by TAZ/PIPC and the underlying risk factors, thereby contributing to the proper use of TAZ/PIPC.

METHODS

Target Patients and Exclusion Criteria This retrospective cohort study was conducted at Shinko Hospital in Hyogo Prefecture, Japan. We targeted inpatients who were treated with TAZ/PIPC for more than three days in our hospital between January and December 2017. Exclusion criteria represented any patient falling under any of the following items: (1) a case without general blood test records, before and after TAZ/PIPC administration, (2) patients with hypokalemia at the start of TAZ/PIPC administration, (3) a case in which a potassium preparation was administered concomitantly at the start of TAZ/PIPC administration, (4) a case in which “medicine stating that the side effect of potassium decline in the package insert or the interview form is 1% or more or frequency unknown” was administered concomitantly during the TAZ/PIPC administration period, (5) patients who received insulin, and (6) a case that received blood purification therapy (BPT), such as continuous renal replacement therapy. Concomitant drug use for exclusion criteria item (4) was confirmed using package inserts and interview forms for each drug as of July 1, 2019.

Survey Items The following data was investigated retrospectively from the electronic charts: Age, sex, body weight (BW), body mass index (BMI), primary medical department, infectious disease name, TAZ/PIPC dose and the number of administration days, serum electrolyte values (serum potassium, serum sodium), serum albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine clearance, as estimated from the formula of Cockcroft & Gault (CLcr), and concomitant drugs. When the serum creatinine level was lower than 0.6 mg/dL, it was calculated by correcting it to 0.6 mg/dL.¹⁴⁾ The value obtained by dividing the daily dosage by the estimated CLcr was then calculated as the “Daily dosage/CLcr”. When “Empirical treatment” was described in the electronic charts or

when no other antibacterial agent was administered before the initiation of TAZ/PIPC administration, it was referred to as “Empirical treatment purpose”. For patients who had the hypokalemia onset, the number of days until hypokalemia was observed for the first time after starting TAZ/PIPC was considered the hypokalemia onset day.

Evaluation Criteria Hypokalemia was evaluated based on the Adverse Event Common Term Standard v4.0 Japan Language Translator JCOG Version (CTCAE v4.0-JCOG). The lowest serum potassium level during TAZ/PIPC administration was classified as grade 1 to grade 2 (serum potassium value < 3.6 – 3.0 mEq/L) and grade 3 to grade 4 (serum potassium value < 3.0 mEq/L). Grade 1 to grade 2 were considered mild hypokalemia (mild group), while grade 3 to grade 4 were considered severe hypokalemia (severe group).

Calculation of the Incidence of Hypokalemia and the Retrieval of Risk Factors The proportion of hypokalemia was determined from the fluctuation of serum potassium levels before and after TAZ/PIPC administration. This calculation was performed according to the following formula: $\text{number of onset} / (\text{number of onset} + \text{number of non-onset}) \times 100 (\%)$. In addition, it was classified according to the dose per day, and the incidence rate with respect to the total number of each administration group was calculated. For each factor investigated, a comparison was made between the groups of hypokalemia onset group and the non-onset group. Univariate logistic regression analysis was performed for each factor. Multivariate logistic regression analysis was subsequently performed using factors that showed statistically significant differences, and the risk factor of hypokalemia onset was examined. Cutoff values were determined by the receiver operating characteristic curve (ROC curve) for continuous variables of factors with significant differences by univariate logistic regression analysis.

Statistical Analysis The Wilcoxon’s signed rank test was used for fluctuation of serum potassium before and after TAZ/PIPC administration. The Pearson’s chi-squared test was used for categorical variables, while the Mann-Whitney *U* test was used for continuous variables comparing the hypokalemic and non-hypokalemic groups. To investigate the risk factors underlying hypokalemia onset, univariate and multivariate logistic regression analyses were per-

Fig. 1. Flowchart of Patient Selection in This Study
TAZ/PIPC: tazobactam/piperacillin.

formed with dependence on the presence or absence of hypokalemia. p -values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS version 23.0.

Ethical Consideration This study was conducted as a single facility retrospective study with approval from our hospital's Ethics Committee (Receipt number: 1813). In addition, we fully respected the protection of personal information by observing the appropriate "ethical guidelines on medical research targeting people".

RESULTS

Target Patient and Patient Backgrounds Of the 795 patients treated with TAZ/PIPC, 375 met exclusion criteria, leaving 420 patients in the study (Fig. 1). There were no patients who received BPT in the target patients. Table 1 shows the patient characteristics. The majority were elderly patients (over 90%). The median of AST, ALT, serum sodium value, and serum potassium value were both within the reference value range. One hundred sixty-seven patients (39.8%) received $4.5 \text{ g} \times 4$ times of TAZ/PIPC a day; 164 patients (39.0%) received $4.5 \text{ g} \times 3$ times a day, and in total, 337 patients (80.2%) received 13.5 g/d or more of TAZ/PIPC. The median (IQR) of the "Daily dosage/CLcr" was 289.6 mg/mL/min (224.8–

399.3 mg/mL/min).

Number of Days to Hypokalemia Onset The distribution of days from TAZ/PIPC administration to hypokalemia onset is shown in Fig. 2. The median time to onset (IQR) was five days (3.3–6 days), with four days (3–6 days) for the mild group and five days (4–6 days) for the severe group. About 22% of the patients developed hypokalemia four days after administration.

Incidence of Hypokalemia and Changes in Serum Potassium Levels The overall incidence of hypokalemia was 24.8%; 18.3% were in the mild group, and 6.4% were in the serious group (Table 2-a). In terms of the daily dosage, the incidence was highest at 30.5% (51/167 patients) in patients given 18 g/d. Focusing on the serious group in particular, the incidence rate increased with dose dependence (Table 2-b). Intergroup comparison results of the factors underlying the hypokalemia onset in the developing group and the non-onset group are shown in Table 3. The incidence of hypokalemia was significantly higher in females than in males. "Age" and "Daily dosage/CLcr" "Number of empirically treated patients" were both significantly higher in the hypokalemic group than in the non-onset group. "BMI", "CLcr", and "pre-administration serum potassium level" were all significantly lower in the

Table 1. Patients' Baseline Characteristics

Background	No. of Patients (%)	Median (IQR)
Age (years)		80.0 (70.0–86.0)
< 60 years	34 (8.1)	51.5 (43.5–55.0)
Sex		
Male	261 (62.1)	
Female	159 (37.9)	
BW (kg)		48.3 (41.6–58.0)
BMI (kg/m ²)		19.7 (16.9–22.2)
Clinical Departments		
Internal Medicine	309 (73.6)	
Pulmonology	108 (25.7)	
General medicine	90 (21.4)	
Hematology	38 (9.0)	
Gastroenterology	35 (8.3)	
Cardiology	17 (4.0)	
Rheumatology	13 (3.1)	
Neurology	6 (1.4)	
Endocrinology and Metabolism	2 (0.5)	
Surgery	111 (26.4)	
Gastrointestinal surgery	51 (12.1)	
Urology	30 (7.1)	
Neurosurgery	17 (4.0)	
Thoracic surgery	5 (1.2)	
Orthopedic surgery	4 (1.0)	
Gynecology	3 (0.7)	
Plastic and Reconstructive surgery	1 (0.2)	
Diagnosis (infectious diseases)		
Pneumonia	87 (20.7)	
Urinary tract infection	80 (19.0)	
Aspiration pneumonia	68 (16.2)	
Abdominal infection	57 (13.6)	
Febrile Neutropenia	39 (9.3)	
Bacteremia/Sepsis	23 (5.5)	
Respiratory infection other than pneumonia	19 (4.5)	
Other infection	47 (11.2)	
Clinical laboratory test values		
ALB (g/dL)		3.1 (2.6–3.5)
AST (IU/L)		22 (16–33)
ALT (IU/L)		16 (11–29)
CLcr (mL/min)		48.5 (33.4–66.7)
Serum sodium (mEq/L)		137 (134–140)
Serum potassium (mEq/L)		4.1 (3.8–4.5)
Medication history		
Dose regimen	Daily dosage (g)	
4.5 g, q6h	18.0	167 (39.8)
4.5 g, q8h	13.5	164 (39.0)
3.375 g, q6h	13.5	6 (1.4)
4.5 g, q12h	9.0	11 (2.6)
2.25 g, q6h	9.0	65 (15.5)
2.25 g, q8h	6.75	7 (1.7)
Duration of administration (d)		7 (5–9)
Daily dosage/CLcr (mg/mL/min)		289.6 (224.8–399.3)
For Empiric therapy		
Yes	324 (77.1)	
No	96 (22.9)	
Companion drug		
Yes	404 (96.2)	
No	16 (3.8)	

IQR: interquartile range, BW: body weight, BMI: body mass index, ALB: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CLcr: creatinine clearance, q6h: every 6 h, q8h: every 8 h, q12h: every 12 h.

Fig. 2. Distribution of Days until Onset of Hypokalemia after Administration of TAZ/PIPC

The onset of hypokalemia was within 7 d in the majority of patients. The median number of days until onset was as follows; Overall: day 5, Severe hypokalemia: day 4, Mild hypokalemia: day 5. ■ Severe hypokalemia, □ Mild hypokalemia.

hypokalemic group than the non-onset group. The fluctuations in serum potassium levels in the non-hypokalemic group and the mild and severe groups, before and after TAZ/PIPC administration, are shown in Fig. 3. In both the mild and severe groups, a significant decrease in the serum potassium level was observed after TAZ/PIPC administration.

Risk Factors of Hypokalemia Univariate and multivariate analyses were performed to search for hypokalemia risk factors (Table 4). Regarding the factors that were found to be significantly different by univariate analysis, “sex (women)”, “age”, “BMI”, “CLcr”, “a serum potassium value before administration”, “Daily dosage/CLcr”, “a purpose except the empiric treatment” were all observed. Further multivariate analysis using these factors indicated “age” ($p < 0.001$, odds ratio 1.057) was a significant hypokalemia risk factor. In contrast, “BMI” ($p = 0.026$, odds ratio 0.925), “pre-serum potassium

level” ($p < 0.001$, odds ratio 0.149), “Except for empirical treatment” ($p = 0.0135$, odds ratio 0.431) were factors significantly reducing hypokalemia risk. Calculating the area under the curve (AUC) of ROC “age” and “Daily dosage/CLcr”, the outcome for hypokalemia occurrence was 0.644 (sensitivity: 0.644, specificity: 0.523) and 0.623 (sensitivity: 0.673, specificity: 0.592), respectively, with the cutoff values of “80.5 years” and “294.9 mg/mL/min”, respectively. The AUC of “BMI” and “serum potassium value before administration” with no hypokalemia were 0.590 (sensitivity: 0.519, specificity: 0.587) and 0.667 (sensitivity: 0.709, specificity: 0.567), respectively, with cutoff values of “19.7 kg/m²” and “3.95 mEq/L”, respectively.

DISCUSSION

In this study, the incidence of grade 3 or higher hypokalemia was 6.4%, which was comparable to the results at the time of the clinical trial for FN patients. However, the incidence rate of mild cases (grade 2 or lower) was 18.3%, which was remarkably high. The incidence of hypokalemia is 26.3% for liposomal amphotericin B, an antifungal drug,¹⁵⁾ and 43.1% for high doses of furosemide, a loop diuretic.¹⁶⁾ Although these medicines are well-known for causing hypokalemia, TAZ/PIPC has comparable incidence rates. Therefore, we may need to alter the perception that hypokalemia is only a rare TAZ/PIPC side effect.

Hypokalemia may occur because of an absorption disorder in the distal renal tubules when large doses of penicillin antibacterial drugs are administered.¹⁷⁾ This mechanism is believed to be due to the fact that penicillin drugs are excreted into tubules as non-absorbable anions and promote excretion of potassium

Table 2. Incidence of Hypokalemia in Patients Administered TAZ/PIPC

Percentage of Hypokalemia %, (No. of Patients)			
a) Overall			
Hypokalemia	24.8% (104/420)		
(Mild)	18.3% (77/420)		
(Severe)	6.4% (27/420)		
b) Classified by Daily Dosage	Mild	Severe	Total
6.75 g ($n = 7$)	14.3% (1/7)	0.0% (0/7)	14.3% (1/7)
9.00 g ($n = 76$)	17.1% (13/76)	3.9% (3/76)	21.1% (16/76)
13.5 g ($n = 170$)	15.3% (26/170)	5.9% (10/170)	21.2% (36/170)
18.0 g ($n = 167$)	22.2% (37/167)	8.4% (14/167)	30.5% (51/167)

Table 3. Comparison between Hypokalemia Group and Non-hypokalemia Group

Factor		Non-Hypokalemia	Hypokalemia	<i>p</i> value
Sex	(Male, <i>n</i> = 261)	205 (64.9%)	56 (53.8%)	0.044 ^{*,a}
	(Female, <i>n</i> = 159)	111 (35.1%)	48 (46.2%)	
Age (years)		77 (68–85)	82 (76–90)	< 0.0001 ^{**,b}
BW (kg)		49.6 (43.6–59.2)	44.1 (38.5–52.6)	< 0.0001 ^{**,b}
BMI (kg/m ²)		19.7 (17.4–22.7)	18.8 (15.9–21.1)	0.006 ^{**,b}
ALB (g/dL)		3.1 (2.7–3.6)	3.1 (2.6–3.5)	0.216 ^b
AST (IU/L)		22.5 (16–33)	21.0 (15–34)	0.380 ^b
ALT (IU/L)		17.0 (11–31)	15.0 (11–26.8)	0.421 ^b
CLcr (mL/min)		50.9 (33.4–69.5)	43.8 (33.2–55.6)	0.014 ^{*,b}
Serum sodium (mEq/L)		137 (134–140)	137 (133–141)	0.827 ^b
Serum potassium (mEq/L)		4.1 (3.9–4.5)	3.9 (3.7–4.2)	< 0.0001 ^{**,b}
Duration of administration (d)		7 (5–9)	8 (5–10)	0.032 ^{*,b}
Daily dosage/CLcr (mg/mL/min)		276.1 (210.0–386.1)	339.4 (271.7–428.8)	0.0002 ^{**,b}
For empiric therapy	Yes (<i>n</i> = 324)	234 (74.1%)	90 (86.5%)	0.009 ^{**,a}
	No (<i>n</i> = 96)	82 (25.9%)	14 (13.5%)	
Companion drug	Yes (<i>n</i> = 404)	303 (95.9%)	101 (97.1%)	0.255 ^a
	No (<i>n</i> = 16)	13 (4.1%)	3 (2.9%)	
Clinical Departments	Internal medicine (<i>n</i> = 309)	226 (71.5%)	83 (79.8%)	0.096 ^a
	Surgery (<i>n</i> = 111)	90 (28.5%)	21 (20.2%)	

BW: body weight, BMI: body mass index, ALB: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CLcr: creatinine clearance. Values are expressed by median (interquartile range) from “Age” to “Daily dosage/CLcr”. ^a Pearson’s chi-squared test, ^b Mann-Whitney *U* test. * or ** significantly different at *p* < 0.05 or *p* < 0.01, respectively.

Fig. 3. Change in Serum Potassium Values from Baseline to after Administration of TAZ/PIPC

Each box shows: upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; horizontal bar within box, median; upper horizontal bar outside box, maximum; lower horizontal bar outside box, minimum. **Significantly different from pre-administration by the Wilcoxon signed-rank test at *p* < 0.01. ns: Not statistically significant.

as a cation.^{11,18)} PIPC is excreted in the urine *via* organic anion transporters (OATs) in the basolateral membranes of the proximal renal tubules.¹⁹⁾ Furthermore, TAZ/PIPC exhibits concentration-dependent inhibitory activity on the substrate uptake of OATs.⁴⁾ Based on these findings, it can be speculated that the incidence of hypokalemia increases, particularly when TAZ/PIPC is administered at a high dose. An

investigation of the incidence of hypokalemia by dose revealed the incidence rate was highest in the patient group administered 18 g/d in this study, followed by 13.5 g/d. However, the “Daily dosage” was not a significant risk factor observed by univariate and multivariate analyses. In many cases, the dose was reduced according to the renal function, and consequently, the “Daily dosage” might not have been a

Table 4. Univariate and Multivariate Analysis of Factors Associated with Hypokalemia by TAZ/PIPC

Variable		Univariate analysis	AUC	Cutoff value	Multivariate analysis		
		<i>p</i> value			Odds ratio	95% CI	<i>p</i> value
Sex	(Male)	—					
	(Female)	0.045*			1.393	0.818–2.371	0.222
Age (years)		<0.001**	0.644	80.5	1.057	1.024–1.090	<0.001**
BMI (kg/m ²)		0.011*	0.590†	19.7	0.925	0.862–0.991	0.026*
ALB (g/dL)		0.193					
AST (IU/L)		0.291					
ALT (IU/L)		0.427					
CLcr (mL/min)		0.009**	0.580†	47.2	1.016	0.997–1.036	0.091
Serum sodium (mEq/L)		0.857					
Serum potassium (mEq/L)		<0.001**	0.667†	3.95	0.149	0.074–0.300	<0.001**
Duration of administration (d)		0.092					
Daily dosage/CLcr (mg/mL/min)		0.006**	0.623	294.9	1.024	1.000–1.049	0.055
Daily dosage	6.75 g	—					
	9.00 g	0.191					
	13.5 g	0.169					
	18.0 g	0.495					
For empiric therapy		—					
Not for empiric therapy		0.009**			0.431	0.221–0.840	0.014*
Companion drug	(–)	—					
	(+)	0.711					

95% CI: 95% confidence interval, BMI: body mass index, ALB: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CLcr: creatinine clearance. * or ** significantly different at $p < 0.05$ or $p < 0.01$, respectively. † Receiver operating characteristic analysis outcome calculated as “Non-Hypokalemia”.

significant risk factor. As related to the reduction of the dose of TAZ/PIPC, there is a report²⁰⁾ that simulated a correlation between the pharmacokinetics and antimicrobial effect of TAZ/PIPC in patients with impaired renal function. With reference to this report, it has been proposed to recommend an optimal daily dosage for patients with impaired renal function.⁴⁾ However, this recommendation is roughly classified into three CLcr of patients and does not focus on the occurrence of side effects. In fact, in this study, some patients developed hypokalemia even at reduced doses. Based on these facts, we consider that the dose for each CLcr should be evaluated in detail and examined using “Daily dosage/CLcr” as an index. The “Daily dosage/CLcr” was significantly higher in the hypokalemic group than in the non-hypokalemic group. Additionally, it was significant in univariate analysis; the cutoff value was 294.9 mg/mL/min. The risk of hypokalemia may increase if it is above the cutoff value for this indicator. However, from multivariate analysis, it was not a significant risk factor in this study. Although “Daily dosage/CLcr” may be an index for evaluating hypokalemia,

our study is not sufficient to make it a useful index. Therefore, various renal functions in patients need to be further verified.

We investigated the day until the hypokalemia onset and observed that it occurred within 6 days and peaked 4 days after the administration. Morimoto *et al.* revealed that acute kidney injury (AKI) by TAZ/PIPC mainly occurred within 1 week after administration.²¹⁾ It is stated that the AKI onset was most frequently 3 days after TAZ/PIPC administration. These findings are roughly similar to the time of hypokalemia onset determined in our study. The other side effects of TAZ/PIPC have not been investigated at this study, however, one or more side effects may occur early after administration. In any case, antimicrobial agents are usually evaluated nearly 3 days after the start of administration, and it may be better to simultaneously confirm the side effects, such as hypokalemia.

Multivariate analysis and ROC analysis revealed age ≥ 80.5 years is a hypokalemia risk factor in TAZ/PIPC-administered patients. Generally, given the lack of nutritional balance in elderly, in addition to

current medical history and the number of medications to be administered, electrolyte anomaly tends to more frequently occur in elderly than in young people.²²⁾ Pharmacokinetics in the elderly are considered to be altered due to decline in physiological functions, for example, renal clearance decreases due to decrease in renal blood flow and glomerular filtration rate, leading to increase in half-life and AUC.²³⁾ Therefore, in particular, renal excretion antibiotics are expected to be greatly affected. Moreover, regarding the distribution of drugs in the body, the concentration of free antibacterial agents, such as penicillin, increases due to decrease in plasma albumin.²³⁾ Because “age” was identified as a risk factor, it was considered that such an elderly-specific pharmacokinetics was significant.

When there is similar extracorporeal loss of potassium, patients of a smaller size tended to have hypokalemia more than those of greater size. This is because potassium capacity is proportional to muscle mass, so the total potassium content in the body tends to be lower for women and those who are thin.³⁾ In addition, hypokalemia usually results from an excessive loss of potassium in the urine or gastrointestinal tract rather than from lower potassium intake. In this study, the incidence of hypokalemia was higher in females than between the onset and non-onset groups, while the “high BMI” significantly prevented the hypokalemia onset. Although the serum ALB level was used to indicate nutritional status, there was no significant difference in serum ALB levels between the non-onset group and onset group. Therefore, body surface area or muscle mass may be related to the background, which became the avoidance factor. Low BMI patients receiving high dose penicillin therapy are at risk of developing severe hypokalemia.²⁴⁾ This is consistent with this study’s results. Also, the higher the “pre-administration serum potassium level” is within the reference value range, or if the administration purpose is “other than empirical treatment”, the possibility of avoiding hypokalemia is suggested. Prior to TAZ/PIPC administration, it is considered that the severity of infection or the amount of bacteria is reduced by the administration of prior antibacterial agent. Therefore, there may be no change in serum potassium levels. In contrast, at the start of empirical treatment, the severity of infection is often high, and the vital signs are often unstable. Therefore, it cannot be denied that hypokalemia

may also be caused by other confounding factors, such as inflammation, and not only by TAZ/PIPC. However, if serum potassium level before TAZ/PIPC administration is <4.0 mEq/L or the BMI is less than 19.7 kg/m², the risk of hypokalemia should be considered.

There are some problems with the results of this study. Because all calculated ROC values were low, it cannot be suggested that the prediction ability is high. Although the ROC values are not large, they are statistically significant. In other words, there is a possibility that the cutoff value can be used as a prediction factor of hypokalemia. However, the purpose of this survey is to find relevancy, not to test the predictive ability. Furthermore, focusing on the target patients, the elderly account for the majority, and the examination of young people is insufficient. Thus, it cannot be concluded that this is true for all TAZ/PIPC-treated patients, including young people. Moreover, “age” was a significant risk factor, but the odds ratio was never high. The influence of TAZ/PIPC administration may not be significant in the hypokalemia onset. These are the results within the scope of this survey. Further additional research, including the verification of predictive ability, is warranted.

This study has the following limitations. (1) This was a retrospective observational study performed in a single facility; thus, it was impossible to completely eliminate the confounding factors. (2) Patients who used drugs, which may have caused potassium elevation, were not excluded, and the study may have included cases that did not appear as hypokalemia. (3) It was impossible to consider conditions and original disease that may have resulted in hypokalemia, such as gastrointestinal bleeding and diarrhea. (4) The type of microorganism being treated was not considered. There was also a possibility that the classification may be incorrect since there are few clear descriptions of “empirical treatment”, which is the purpose of administering TAZ/PIPC in the medical record. In the future, to solve these problems, we believe it is necessary to examine these issues more comprehensively by conducting cooperative prospective cohort research with other facilities.

Collectively, our findings suggest that although multiple entanglements are assumed, the incidence of hypokalemia in TAZ/PIPC-administered patients is higher than expected. Additionally, as a newly disco-

vered important finding, it was revealed that the risk factor of hypokalemia onset under TAZ/PIPC administration is age. These findings could provide important information for the safe administration of TAZ/PIPC and can be considered useful for promoting proper use of TAZ/PIPC.

CONCLUSION

This study retrospectively analyzed the frequency of hypokalemia in TAZ/PIPC-administered patients and its risk factors. As a result, the incidence of hypokalemia was found to be as high as 20%, including mild cases. Consequently, by confirming “age”, “BMI”, “serum potassium level”, and “administration purpose” before TAZ/PIPC administration, we believe that the risk of hypokalemia should be recognized early. In addition, monitoring serum potassium levels is necessary during the administration, requiring special attention 3–6 days after the administration.

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Conflict of Interest The authors declare no conflict of interest.

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