


Effects of dosing frequency on the clinical efficacy of ampicillin/sulbactam in Japanese elderly patients with pneumonia: A single-center retrospective observational study

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Abstract

This study sought to investigate whether dosing frequency (the number of doses per day) affects the antimicrobial efficacy and safety of ampicillin/sulbactam (ABPC/SBT) in Japanese elderly pneumonia patients treated with ABPC/SBT at 6 g/day. This was a retrospective observational study that included hospitalized elderly patients (aged ≥ 75 years, 10 ml/min \leq CLcr < 50 ml/min) who received 3 g every 12 h (BID; $n = 61$) or 1.5 g every 6 h (QID; $n = 45$) for the treatment of pneumonia. The primary endpoint was clinical response, assessed by measuring body temperature, white blood cell count, and C-reactive protein levels. Pharmacokinetic and pharmacodynamic simulations were conducted *in silico* to rationalize the clinical findings. The clinical response rates (extremely effective and effective) in the BID and QID groups were 36.1% and 55.6%, respectively ($p = .0459$). QID tended to be more effective in patients with gram-negative rods detected ($p = .0563$). According to the simulated minimum plasma ABPC concentrations at steady state for BID and QID were 2.5 and 7.3 $\mu\text{g/ml}$, respectively ($p < .0001$). Based on the simulated time above minimum inhibitory concentration (MIC), pharmacological (not clinical) efficacy was predicted to be higher with QID. Both groups had similar safety profiles. The main adverse event in both groups was liver damage. The present retrospective survey demonstrated that ABPC/SBT treatment for elderly patients with pneumonia and renal dysfunction was more effective with QID than with BID. Therefore, the QID regimen is worthy of consideration to improve the clinical outcomes of ABPC/SBT therapy in the present patient population.

KEYWORDS

ampicillin/sulbactam, elderly patients, pharmacokinetics-pharmacodynamics, pneumonia, retrospective study

Abbreviations: ABPC, ampicillin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLcr, creatinine clearance; CRP, C-reactive protein; GGT, γ -glutamyl transferase; GNR, gram-negative rod; GPC, gram-positive cocci; MIC, minimum inhibitory concentration; PTA, probability of target attainment; SBT, sulbactam; WBC, white blood count.

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1 | INTRODUCTION

Pneumonia is a critical disease affecting the life prognosis of elderly people.¹ Generally, the elderly show lower drug clearance as they have reduced renal or hepatic function, primarily caused by aging-induced changes in physiological functions, often necessitating the reduction of drug dosage for this population.

Ampicillin (ABPC)/sulbactam (SBT), one of the first-line treatments for pneumonia,¹ is a product of ampicillin sodium and sulbactam sodium combined at a dose ratio of 2:1. ABPC has potent and broad-spectrum bactericidal activity against gram-positive and -negative aerobic and anaerobic bacteria, such as *Escherichia coli* (*E. coli*), *Proteus mirabilis*, and *Haemophilus influenzae* (*H. influenzae*). Meanwhile, SBT extends the antibacterial spectrum to include many ABPC-resistant bacteria by inhibiting the plasmid-mediated β -lactamase responsible for the transfer of drug resistance, such as that from *Proteus vulgaris*, *Acinetobacter* species (sp.), and *Bacteroides* sp.^{2,3}

The recommended dosage of ABPC/SBT for pneumonia treatment in patients with normal renal function is 3 g four times per day.^{1,4} ABPC and SBT reversibly bind to human serum proteins with reported binding activity of approximately 28% and 38%, respectively.⁵ Both drugs are primarily eliminated via urine excretion, mostly through glomerular filtration and urinary tubular secretion,^{6,7} therefore, the dose of ABPC/SBT must be adjusted depending on the renal function of the patient. The antimicrobial activity of β -lactam antibiotics, such as penicillins, cephalosporins, and carbapenems, depends on the time that serum drug concentrations remain above the minimum inhibitory concentration (MIC) (time above MIC, T > MIC). This pharmacokinetic–pharmacodynamic (PK-PD) parameter is considered to be a better predictor of antimicrobial efficacy, including that in terms of bacteriological eradication rate and clinical outcome.^{8,9} The PK-PD theory recommends increasing the number of doses per day for the fixed daily dose of β -lactams, such as ABPC/SBT.¹ The recommended maximum dosage of ABPC/SBT for pneumonia patients with normal renal function is 3 g every 6 h. For patients with impaired renal function, the daily dose is reduced, and the dosage of ABPC/SBT (6 g/day) is commonly recommended at 3 g every 12 h to avoid increased exposure to the drug.¹⁰ However, in some cases, ABPC/SBT is occasionally administered at 1.5 g every 6 h. Moreover, there are currently no reports comparing the effects of different dosing frequencies on the efficacy of ABPC/SBT administered at a fixed dose of 6 g/day. Therefore, this retrospective study aimed to investigate the effect of dosing frequency (the number of doses per day) on the efficacy and safety of ABPC/SBT treatment in elderly pneumonia patients treated with a reduced dose of ABPC/SBT (6 g/day) owing to impaired renal function (creatinine clearance; 10 ml/min \leq CLCr < 50 ml/min). The dosage recommended in the textbook (3 g every 12 h; BID)¹⁰ and the dosage considered to be appropriate based on the PK-PD theory (1.5 g every 6 h; QID) were compared in terms of efficacy and safety. Moreover, using the model established by Soto et al.,⁵ we simulated the time profiles for ABPC plasma concentrations and the T>MIC to comparatively predict their clinical efficacies.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

We performed a single-center retrospective observational study at the Japan Community Health care Organization Tokyo Takanawa Hospital (Tokyo Takanawa Hospital). Patients with 10 ml/min \leq CLCr < 50 ml/min who were 75 years or older, and admitted to Tokyo Takanawa Hospital between April 1, 2016 and March 31, 2019, were eligible for this study. CLCr values were estimated using the Cockcroft–Gault formula.

ABPC/SBT (SULBACILLIN™ 1.5 g for Injection; Meiji Seika Pharma Co., Ltd. Japan) was administered at a daily dose of 6 g (ABPC 4 g/SBT 2 g) via intravenous drip for the treatment of pneumonia, including community-acquired pneumonia, aspiration pneumonia, or nosocomial-acquired pneumonia during treatment for other diseases (all the patients were diagnosed with pneumonia by the attending physician). The daily dosing frequency of ABPC/SBT was 3 g twice per day (BID) or 1.5 g four times per day (QID).

The exclusion criteria included (a) discontinuation due to hypersensitivity, (b) death due to non-pneumonia disease, (c) discontinuation due to severe adverse events caused by other drugs, and (d) discontinuation of ABPC/SBT treatment due to the difficulty associated with intravenous administration, poor prognosis of the primary disease, or adverse events such as liver and renal dysfunctions.

The clinical response, as the primary endpoint of this retrospective study, was assessed by assessing body temperature, white blood cell (WBC) count, C-reactive protein (CRP), X-ray (or CT) findings, and clinical signs or symptoms of pneumonia according to the criteria for the evaluation of effectiveness in clinical efficacy recommended by the Japanese Society of Chemotherapy with some modification.¹¹ Clinical outcome was evaluated if improvement was observed in two or three of the following criteria: (1) fever resolution (body temperature \leq 37°C); (2) normalized WBC count (< 9000 /mm³); (3) improved CRP (30% or more reduction from baseline). When only two items were achieved, those without exacerbation of the remaining item were evaluated as the clinical outcome. Moreover, “effective” was classified into two levels: 1. extremely effective; 2. effective, which were defined as achievement of the criteria within 3 days (day 4) or 7 days (day 8) from initiation of ABPC/SBT treatment, respectively. The clinical response rate was calculated as the percentage of patients exhibiting “extremely effective” and “effective” outcomes. Cases that did not achieve the criteria, or that were determined to have no effect by the attending physician within 3 days, resulting in termination of the ABPC/SBT treatment, were evaluated as “ineffective.”

2.2 | Patient data

All patient data were collected using the electronic medical record system of Tokyo Takanawa Hospital (MegaOak HR, NEC Co., Ltd.

Japan). Patient background data included sex, body weight (kg), height (cm), body mass index (BMI; kg/m²), age (year), CURB-65 score,¹² total protein (g/dl), serum albumin (g/dl), serum creatinine (mg/dl), blood urea nitrogen (mg/dl), CLcr (ml/min), total bilirubin (mg/dl), alanine aminotransferase (ALT; IU/L), aspartate aminotransferase (AST; IU/L), γ -glutamyl transferase (GGT; IU/L), Na (mEq/L), K (mEq/L), Cl (mEq/L), WBC ($\times 10^3/\mu\text{l}$), CRP (mg/dl), and body temperature ($^{\circ}\text{C}$). Culture data included MIC ($\mu\text{g/ml}$), clinical findings, ABPC/SBT administration days, and type of antibiotics administered before and after ABPC/SBT. The MIC values of ABPC/SBT or ABPC were determined for the identified microorganisms using the broth microdilution method based on the Clinical and Laboratory Standards Institute (CLSI) procedure. All bacteriological tests were performed in the medical laboratory of Tokyo Takanawa Hospital. The study protocol was approved by the Ethics Committees of Tokyo Takanawa Hospital (No 2017–018) and was performed in accordance with the Declaration of Helsinki. All data were handled anonymously to protect patients' privacy and confidentiality.

2.3 | PK-PD simulations

Plasma ABPC concentrations after treatment with each dosing regimen were estimated from individual values of body weight and CLcr using the population PK model established by Soto et al.⁵ and NONMEM software (ver. 7.2; Icon Development Solutions, Ellicott City, MD, USA).

The population PK model consists of two compartments with the covariates of CLcr on total clearance (CL) and body weight on peripheral volume (V2), as demonstrated in Equations (1)–(4). The parameters containing “i” indicate individual parameters, whereas those that are unmarked indicate a typical parameter.

$$CL_i = CL \cdot \left(\frac{CLcr_i}{71} \right)^{\theta_{CLcr}} \cdot \exp(\eta_{CLi}) \quad (1)$$

$$V1_i = V1 \quad (2)$$

$$Q_i = Q \quad (3)$$

$$V2_i = V2 \cdot \left(\frac{BW_i}{51} \right)^{\theta_{BW}} \cdot \exp(\eta_{V2i}) \quad (4)$$

Where CL represents clearance, V1 is central volume, V2 is peripheral volume, BW is body weight, Q is inter-compartment clearance, θ is the scale factor, and η represents the individual random effect with mean zero and variance.⁵

PK-PD simulations were performed using SAS software (ver. 8.2; SAS Institute Japan Ltd., Japan). The mean ABPC plasma concentration versus time profile was plotted, and the area under the plasma concentration–time curve from 0 to 24 h ($AUC_{0-24\text{h}}$) at steady state, maximum concentration (C_{max}), and minimum concentration (C_{min}) were calculated for BID and QID. The simulation was performed for

each patient using the individual renal function and dosing regimen, and the time intervals in which the plasma concentration exceeded a given MIC value per day ($T > MIC$) were calculated. The probability of target attainment (PTA) for a dosing regimen was further calculated as the ratio of patients receiving $f \cdot T > MIC$ of 40% for a given MIC, where f represents the unbound fraction of ABPC in plasma (i.e., 0.72). The PTA values were assessed as the predictor of drug activities, that is, static effect, bactericidal effect, and clinical outcome,^{13–16} and plotted against the MIC range. The range of MIC employed for the simulation ranged from 0.06 to 32 $\mu\text{g/ml}$, considering the sputum culture results of this study and the data obtained for the main pathogen of pneumonia at Tokyo Takanawa Hospital during the same period of this study.

2.4 | Safety assessment

Safety data were obtained based on clinical signs and symptoms, physical examination, vital signs, and laboratory tests. All adverse events were recorded regardless of suspected causal relationship to ABPC/SBT administration and evaluated according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE v5.0).

2.5 | Statistical analysis

Statistical analysis was performed using JMP Pro 14.0 for Mac (SAS Institute Japan Ltd., Japan) to compare the BID and QID groups. A two-sided p value of $< .05$ indicated significance. Parametric and nonparametric continuous variables were analyzed with Student's t -test and Wilcoxon rank-sum test, respectively. Chi-squared test or Fischer's exact test was used for ordinal and nominal variables.

3 | RESULTS

3.1 | Patient characteristics

A total of 106 elderly subjects with pneumonia (age ≥ 75 years, 10 ml/min \leq CLcr < 50 ml/min) were recruited (Figure 1). The BID and QID groups consisted of 61 and 45 patients, respectively. The median age was 89 and 88 years and the median CLcr was 32.1 and 34.4 ml/min, respectively, in the BID and QID groups. The total bilirubin level in the QID group was significantly higher than that in the BID group (0.5 vs. 0.4 mg/dl, $p = .02$). The other parameters did not differ significantly between the two groups (Table 1). A total of 17 different causal pathogens were identified at baseline (Table 2).

3.2 | Clinical response

The clinical response rate was investigated in both groups (Table 3). The observed response rate in the BID group was 36.1% (22/61

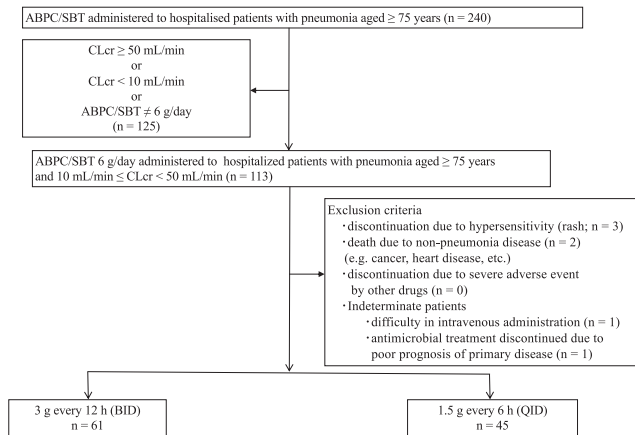


FIGURE 1 Flow of patient selection applied for this retrospective study. ABPC/SBT: ampicillin/sulbactam, CLcr: creatinine clearance

patients), whereas that in the QID group was 55.6% (25/45 patients; $p = .0459$).

We further investigated the relationship between sputum culture data and clinical response (Table 4). The number of patients examined for sputum culture was 37 and 33 in the BID and QID groups, respectively. Oral normal flora was only detected in 10 patients in both groups. The number of patients with a single pathogen was 14 and 11 in the BID and QID groups, respectively. The response rate of patients with only normal flora was significantly higher in the QID group than in the BID group (80% vs. 20%, $p = .0062$). The response rate against gram-positive cocci (GPC) in the BID group was as effective as that in the QID group (55.6% vs. 50.0%), and that against gram-negative rod (GNR) bacteria in the QID group tended to be higher than that in the BID group (42.1% vs. 21.9%, $p = .0563$).

3.3 | PK-PD simulations

Plasma concentrations of ABPC were simulated using the two-compartment model for subjects who received repeated intravenous infusions of 1.5 g or 3 g ABPC/SBT for 30 min (Figure 2). As shown in Table 5, the C_{\min} of ABPC in the QID was significantly higher than that in the BID after 96 h ($p < .0001$). The C_{\max} of ABPC for BID was significantly higher than that for QID on day 4 ($p < .0001$).

ABPC has been found to be reversibly bound by approximately 28% to human serum protein.⁵ Unbound drugs are generally considered to represent pharmacological efficacy; therefore, we also calculated the concentrations of unbound ABPC and evaluated the antibiotic efficacy (Table 6). The ratio of $T > \text{MIC}/24$ h of the QID on day 4 was significantly higher than that of BID (0.72 ± 0.21 vs. 0.53 ± 0.18 , $p < 0.001$). Subsequently, we calculated the ratio $>40\%$ of the $T > \text{MIC}$, namely the PTA (Figure 3). In the QID group nearly all cases achieved the PTA when the MIC value was 8 $\mu\text{g}/\text{ml}$. However, at concentrations above 8 $\mu\text{g}/\text{ml}$, it decreased sharply. In the BID group, however, the PTA decreased at MICs over 4 $\mu\text{g}/\text{ml}$. In the MIC

TABLE 1 Patient characteristics at baseline

Characteristic	BID (n = 61)	QID (n = 45)	p value*
	median (range)	median (range)	
Male/female	26/35 (male 42.6%)	19/26 (male 42.2%)	
Age (year)	89 (75–101)	88 (76–103)	.43
Body weight (kg)	40.9 (23–78)	39.3 (25–78.5)	.42
BMI (kg/m ²)	17.8 (12.1–34.2)	17.1 (11.6–32.7)	.09
Cr (mg/dL)	0.92 (0.4–2.3)	0.85 (0.42–1.48)	.19
CLcr (ml/min)	32.1 (11.4–49.8)	34.4 (15.5–49.7)	.19
T-Bil (mg/dL)	0.4 (0.2–1.4)	0.5 (0.2–3.3)	.02
ALT (U/L)	14 (2–301)	14 (5–56)	.83
AST (U/L)	22.5 (10–208)	26 (9–63)	.44
G-GT (U/L)	23 (5–161)	24 (8–254)	.43
Alb (g/dL)	2.8 (1.6–3.9)	2.9 (1.5–3.8)	.35
BUN (mg/dL)	20.5 (5.2–86.1)	22.3 (6.3–67.2)	.76
CURB-65 score ^a (1/2/3/4/5)	8/17/22/12/2	10/11/12/10/2	.68**
Body temperature (°C)	37.8 (35.2–39.9)	37.7 (35.3–40.4)	.84
CRP (mg/dL)	7.15 (0.27–22.99)	6.81 (0.36–19.0)	.71
WBC (cells/ μL)	9300 (3840–40000)	9560 (3620–25620)	.68
Days of ABPC/SBT administration	9 (2–23)	8 (2–40)	.70

Abbreviations: Alb, serum albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Cr, serum creatinine; CRP, C-reactive protein; WBC, white blood cell; G-GT, γ -glutamyl transferase; T-Bil, total bilirubin.

Data represent median (range) or n (%), unless otherwise indicated. CURB-65 = confusion, urea, respiratory rate, blood pressure, age >65 years.

^aOne point each is assigned for the findings of confusion, blood urea nitrogen greater than 19 mg/dl, respiratory rate of more than 30 breaths per min, systolic blood pressure less than 90 mmHg or diastolic blood pressure of 60 mmHg or less, and age of 65 years or older.

*Wilcoxon rank-sum test.

**Fisher's exact test.

range of 4–16 $\mu\text{g}/\text{ml}$, the PTA values were significantly higher in the QID group than in the BID group.

3.4 | Safety assessment

Based on the collected clinical records, the adverse events were not significantly different between the two groups (Table 7). The proportion of patients with grade 3 or worse adverse events was 31% of 61 patients in the BID group and 31% of 45 patients in the QID group. One patient in the QID group experienced a grade 3 AST increase and ALT increase. Electrolyte abnormalities were observed in few patients in both groups as shown in Table 7.

TABLE 2 Pathogens isolated from the sputum baseline culture

		BID (n = 61)	QID (n = 45)			BID (n = 61)	QID (n = 45)
Patients with baseline pathogen		37	33				
Isolated pathogen	MIC (µg/ml)	No. of patients		Isolated pathogen	MIC (µg/ml)	No. of patients	
Normal flora		10	10	Gram-negative bacteria			
Gram-positive bacteria				<i>K. pneumoniae</i>	4	1	
<i>S. aureus</i> (MSSA)	4	1			8	3	5
	8	3	6		16	2	
<i>S. aureus</i> (MRSA)	8	2	3		>16	1	
	16	1	2	<i>K. pneumoniae</i> (ESBL)	>16	1	
<i>S. pneumoniae</i> (MIC of ABPC)	0.06		2	<i>K. oxytoca</i>	4	1	
	0.5	1	1		8	2	1
<i>S. pneumoniae</i> (urine antigen test positive alone)		3			16	1	
				<i>K. aerogenes</i>	8		1
<i>S. dysgalactiae</i>	Susceptible	1		<i>E. coli</i>	8		1
<i>S. agalactiae</i> (Group B) (MIC of ABPC)	0.12		2		>16	1	2
				<i>E. coli</i> (ESBL)	16		1
					>16	2	
				<i>P. aeruginosa</i>		6	5
				<i>H. influenzae</i>	0.5	1	
				<i>H. parahaemolyticus</i>	2		1
				<i>M. catarrhalis</i> (MIC unknown)			2
				Others (5 species)		10	3

S. aureus: *Staphylococcus aureus*, *S. pneumoniae*: *Streptococcus pneumoniae*, *S. dysgalactiae*: *Streptococcus dysgalactiae*, *S. agalactiae*: *Streptococcus agalactiae*, *K. pneumoniae*: *Klebsiella pneumoniae*, *K. oxytoca*: *Klebsiella oxytoca*, *K. aerogenes*: *Klebsiella aerogenes*, *E. coli*: *Escherichia coli*, *P. aeruginosa*: *Pseudomonas aeruginosa*, *H. influenzae*: *Haemophilus influenzae*, *H. parahaemolyticus*: *Haemophilus parahaemolyticus*, *M. catarrhalis*: *Moraxella catarrhalis*, MSSA: methicillin-susceptible *S. aureus*, MRSA: methicillin-resistant *S. aureus*, ESBL: extended-spectrum β -lactamase.

TABLE 3 Comparison of clinical response and clinical response rate between the BID and QID groups

	BID (n = 61)	QID (n = 45)	p value*
Clinical response, n (%)			.0223*
Extremely effective	8 (13.1)	14 (31.1)	
Effective	14 (23.0)	11 (24.4)	
Ineffective	39 (63.9)	7 (44.4)	
Clinical response rate ^a	36.1%	55.6%	.0459**

^aClinical response rate was defined as the percentage of patients who showed extremely effective + effective.

*Wilcoxon rank-sum test.

**Chi-squared test.

4 | DISCUSSION

ABPC/SBT has been widely used to treat patients with pneumonia. The efficacy and pharmacokinetics of ABPC/SBT (3 g twice per day) have been evaluated in several clinical studies on elderly patients or patients

with renal dysfunction.^{16,17} This study is the first to compare the clinical efficacy of ABPC/SBT (6 g/day) between the BID regimen (3 g every 12 h), which is recommended by textbooks and package inserts,^{10,18} and the QID regimen (1.5 g every 6 h), which is considered preferable to increase T>MIC. We conducted a retrospective observational study on the clinical efficacy of ABPC/SBT treatment with BID and QID regimens in elderly pneumonia patients aged 75 years and older with 10 ml/min \leq CLCr <50 ml/min. There were no patients with treatment of ABPC/SBT at the dosage of 2 g every 8 h (TID), so that we did not compare the TID regimen with others.

At baseline, total bilirubin levels were significantly different between the two groups (Table 1). However, ABPC and SBT are not readily metabolized but rather are excreted via the kidney, with the urinary excretion rate of unchanged drugs approximately 80%.^{5,6} The generated metabolites, if any, are known to have no antimicrobial activity.⁷ Therefore, the PK-PD of ABPC/SBT is not significantly altered owing to the differences in hepatic function and degree of hepatic damage. Thus, the abovementioned difference in the total bilirubin level between the two groups was considered not to impact the effectiveness of pneumonia treatment.

TABLE 4 Comparison of clinical response rate between the BID and QID groups depending upon various pathogens

	BID (n = 37)	QID (n = 33)	p value*
Normal flora	2/10 (20%)	8/10 (80%)	.0062
Gram-positive cocci	5/9 (55.6%)	8/16 (50.0%)	.6028
<i>Streptococcus pneumoniae</i>	1/1	2/3	
<i>Streptococcus dysgalactiae</i>	0/1	—	
<i>Streptococcus agalactiae</i>	—	1/2	
<i>Staphylococcus aureus</i> (with MRSA)	4/7	5/11	
MRSA	1/3	1/5	
Gram-negative cocci	—	1/2 (50%)	
<i>Moraxella catarrhalis</i>	—	1/2	
Gram-negative rods	7/32 (21.9%)	8/19 (42.1%)	.0563
<i>Haemophilus influenzae</i>	0/1	—	
<i>Haemophilus parahaemoliticus</i>	—	0/1	
<i>Stenotrophomonas maltophilia</i>	0/2	—	
<i>Klebsiella pneumoniae</i>	4/8	3/5	
<i>Klebsiella oxytoca</i>	1/4	1/1	
<i>Escherichia coli</i>	1/3	1/3	
<i>Serratia marcescens</i>	0/1	—	
<i>Citrobacter koseri</i>	1/1	—	
<i>Enterobacter cloacae</i>	0/5	1/2	
<i>Enterobacter aerogenes</i>	—	0/1	
<i>Proteus mirabilis</i>	0/1	0/1	
<i>Pseudomonas aeruginosa</i>	1/6	2/5	

Clinical response rate is Extremely effective +Effective.

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

*Wilcoxon rank-sum test.

This study firstly revealed that ABPC/SBT treatment was more effective with QID (1.5 g every 6 h) than with BID (3 g every 12 h) in elderly patients with pneumonia and renal dysfunction, based on early improvement of pneumonia by day 8 (Table 3). As shown in Table 4, the analysis of the relationship between clinical response and isolated pathogen groups (e.g., GPC and GNR) showed no difference in the clinical response to GPC between the BID and QID groups. However, the clinical response to GNR in the QID group tended to be better than that in the BID group. Penicillin antibiotics generally have potent antimicrobial activity against GPC, and weak antimicrobial activity against GNR. According to the CLSI guidelines,¹⁹ the breakpoint of many GPC is less than 1 µg/ml for ABPC. In this study, the MIC of ABPC was 0.5 µg/ml or less for all isolated streptococci and 0.12 µg/ml or less for half of the isolated *S. aureus* (not including MRSA), among GPC (data not shown). Alternatively, the breakpoint of many GNRs, including Enterobacteriaceae, is 8 µg/ml or less for ABPC/SBT.¹⁹ Due to the higher MIC, higher concentrations should be required to achieve T>MIC >40% against GNR; therefore, it was considered that the

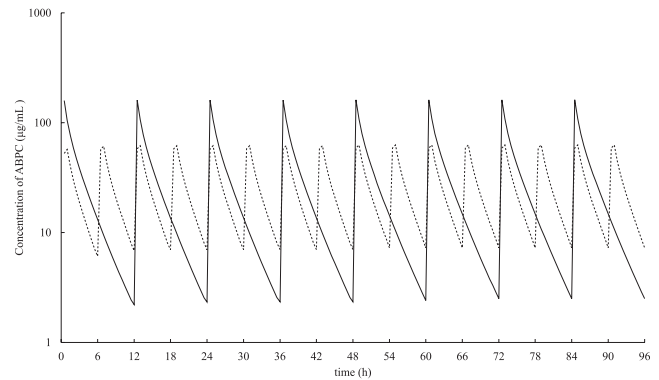


FIGURE 2 Simulated plasma concentration–time profiles of ABPC (BID vs. QID). A population pharmacokinetic model⁵ was employed to simulate the plasma ampicillin concentrations after initiating 1.5 g ABPC/SBT intravenous treatment every 6 h, or 3 g every 12 h (30-min intravenous infusion). Straight line represents BID mean (n = 61), and dotted line represents QID mean (n = 45)

TABLE 5 Comparison of C_{min} and C_{max} values of ABPC in plasma by pharmacokinetic simulations between the BID and QID groups

	BID (n = 61)	QID (n = 45)	p value*
C _{min} (µg/ml) 96 h	2.5 ± 3.9	7.3 ± 5.1	p < .0001
C _{max} (µg/ml) Day 4	161.7 ± 9.9	62.8 ± 10.6	p < .0001

Plasma concentrations of ABPC were simulated using the two-compartment population PK model⁵ for subjects who received repeated intravenous infusions of 3 g (BID) or 1.5 g (QID) ABPC/SBT for 30 min. Mean ± SD.

*Wilcoxon rank-sum test.

TABLE 6 Ratio of time above MIC for 24 h on day 4

MIC (µg/ml)	BID (n = 61)	QID (n = 45)	p value*
0.06	0.993 (0.030)	1 (0)	.1331
0.125	0.989 (0.049)	1 (0)	.1331
0.25	0.976 (0.070)	1 (0)	.0046
0.5	0.945 (0.100)	1 (0)	<.0001
1	0.889 (0.141)	0.998 (0.012)	<.0001
2	0.796 (0.172)	0.972 (0.066)	<.0001
4	0.670 (0.181)	0.883 (0.143)	<.0001
8	0.525 (0.180)	0.717 (0.213)	<.0001
16	0.373 (0.149)	0.465 (0.180)	.0071
32	0.223 (0.103)	0.233 (0.093)	.3806

Mean (SD).

*Wilcoxon rank-sum test.

QID group showed better clinical response compared with the BID group, especially against GNR. The QID regimen was significantly more effective on patients with oral normal flora only (p = .0062) (Table 4). Oral normal flora, which is considered to be

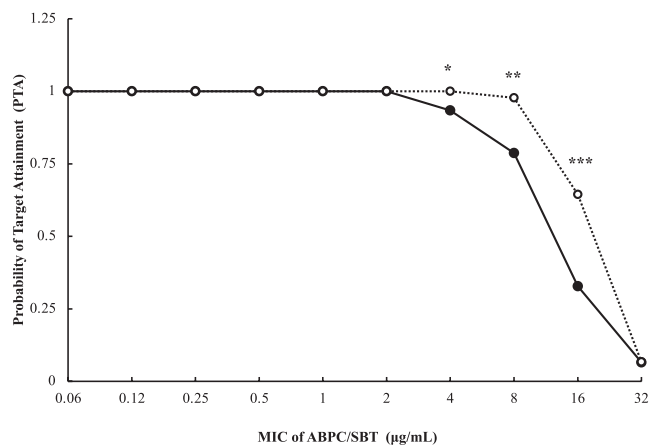


FIGURE 3 Probability of target attainment (PTA) for ABPC/SBT. Achieving 40% $f \cdot T > MIC$ for 24 h as simulated unbound plasma ABPC concentration following multiple 30 min intravenous infusions of 1.5 g or 3 g ABPC/SBT at day 4. Protein bound ratio 28%. * $p = .0332$, ** $p = .0016$, *** $p = 0.0011$ as determined by Chi Square test. Closed circles represent BID ($n = 61$) and open circles are QID ($n = 45$). Both symbols overlap at an MIC range $< 2 \mu\text{g/ml}$

TABLE 7 Safety assessment of BID vs. QID

	CTCAEv5.0 grade (1/2/3/4)		
	BID ($n = 61$)	QID ($n = 45$)	p value*
Increased T-Bil	4/1/0/0	3/0/0/0	.71
Increased AST	14/0/1/0	8/1/1/0	.62
Increased ALT	9/1/0/0	5/1/1/0	.65
Increased GGT	2/0/0/0	3/0/0/0	.45
Increased Cr	7/1/0/0	5/1/0/0	.97
Hypoalbuminemia	5/32/9/0	3/23/6/0	.76
Hyperkalemia	4/0/1/0	4/0/0/0	.63
Hypernatremia	0/4/1/0	2/0/1/1	.10
Hypokalemia	12/0/5/1	7/0/4/0	.77
Hyponatremia	9/2/1/0	5/2/0/0	.77

*Chi-squared test.

causative organisms of aspiration pneumonia, generally consists of various kinds of bacteria including Gram-negative bacteria. Since the QID regimen could induce higher trough concentrations of ABPC, gram-negative bacteria among normal flora could be affected more in the QID group. Moreover, it was considered that the causative pathogens of nosocomial pneumonia often have reduced antimicrobial susceptibility.²⁰⁻²² Therefore, administration of ABPC/SBT according to the QID regimen may be more effective, particularly for nosocomial-acquired cases of pneumonia. In this study, the clinical response was observed in some cases with *p. aeruginosa*, which is ineffective with ABPC/SBT (Table 4). This may have been due caused by concomitant infection with other pathogens.

The previous multicenter study performed by Soto et al.⁵ from which we adopted the population PK model in this study, was performed in Japanese patients, and the range of their patient background (age, body weight, BMI, serum creatinine, and CLcr) overlapped with that of this study. Therefore, the use of this PK model and its parameters was considered adequate in the present population.

A longer $T > MIC$ is considered important for penicillins (β -lactams), including ABPC, to maintain their antimicrobial activity.^{8,14,15} The present PK-PD simulations showed that the minimum plasma concentration of ABPC in the QID group was higher than that in the BID group (Figure 2; Table 5), whereas the ratio of $T > MIC$ (0.25–16 $\mu\text{g/ml}$) for the QID group was significantly higher than that for the BID group (Table 6). Moreover, the $T > MIC$ of β -lactams, including penicillins, must exceed 40% against the administration interval to achieve the static effects or maximal bactericidal effects.^{8,15} Therefore, the PTA, which is the percentage of patients achieving $f \cdot T > MIC$ (%) of 40% for a given MIC, is considered to be a target index of clinical efficacy. We, therefore, calculated the PTA values of various MICs and found that in the QID group it was significantly higher than that in the BID group (Figure 3). Although the Sanford Guide recommends ABPC/SBT therapy with the BID regimen (3 g every 12 h) for pneumonia patients with renal dysfunction,¹⁰ the present results suggest that the QID regimen, compared with the BID regimen, was preferable for elderly patients with reduced renal function to obtain better clinical outcomes.

However, QID and BID were not significantly different in terms of safety (Table 7), and showed no significant differences in the incidence of adverse events, according to comparisons between the present findings and the package insert of Unasyn[®] (Pfizer Japan Inc. Tokyo, Japan).¹⁸ Therefore, this study showed that ABPC/SBT could be safely administered at 1.5 g every 6 h in elderly patients with pneumonia aged 75 years and older with $10 \text{ ml/min} \leq \text{CLcr} < 50 \text{ ml/min}$.

According to a previous report⁴ the response rate at the end of ABPC/SBT treatment (12 g/day) in patients with normal renal function is approximately 90%; meanwhile, in this study, the response rate by day 8 was only 55.6% in the QID group. This study examined patients with impaired renal function who received ABPC/SBT at 6 g/day, however, given the low response rate, some patients may have required the higher daily dose and the longer $T > MIC$. In fact, the 2019 revision of the Sanford Guide to antimicrobial therapy recommended daily dose for patients with impaired renal function (30 ml/min and above) was revised to 9 g, which is accordance with the present results.

There are, however, certain limitations noted in this study. First, this study was a retrospective observational study, not a prospective randomized control study. Therefore, the data of PK-PD simulation were numerical values calculated *in silico*, and all values of ABPC concentrations were not obtained by actual measuring of the drug blood concentrations using a patient's blood samples. Second, there

were only 106 patients in both groups, and this sample size is considered relatively small for a retrospective observational study. For this reason, sub-group analyses depending on patients' characteristics such as renal function, severity of pneumonia, and concomitant medications were not performed. Third, the TID regimen was not evaluated.

In conclusion, this study was the first to suggest that ABPC/SBT treatment was more effective with QID (1.5 g every 6 h) than BID (3 g every 12 h) in elderly patients with pneumonia and renal dysfunction, and the two regimens had similar safety profiles. The PK-PD simulations further supported our findings. Hence, the QID regimen is worthy of consideration to improve the clinical outcomes of ABPC/SBT therapy in the present patient population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORSHIP STATEMENT

All authors meet the ICMJE authorship criteria. Tomokazu Suzuki designed the study and contributed to data collection, analysis, and interpretation of the data. Kyoka Takahashi assisted in the data collection. Kenji Nozawa contributed to simulate PK-PD. All other authors contributed data interpretation and critically reviewed the manuscript. All authors contributed to the writing of the final manuscript and approved it for publication. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The research data are not shared.

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