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A Clinical Comparative Study of Piperacillin and Sulbactam/Ampicillin in Patients with Community-Acquired Bacterial Pneumonia

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Abstract

Objective To evaluate the clinical usefulness of piperacillin (4 g/day) therapy for community-acquired pneumonia compared to sulbactam/ampicillin (6 g/day).

Methods A randomized prospective clinical study was conducted in patients with mild to severe community-acquired bacterial pneumonia.

Results The overall clinical efficiency of piperacillin therapy (4 g/day) in these patients (41/53=77.4%) was comparable to that of sulbactam/ampicillin therapy (6 g/day: efficiency rate: 33/49=67.3%), when each therapy was administered intravenously for 3-7 days. With regards to clinical efficiency based on disease severity, bacteriological efficiency, improvement in chest X-ray findings and adverse reactions, the two therapies were comparable, even though we found more efficiency for patients who had underlying diseases and there were also cost benefits in piperacillin therapy, compared with sulbactam/ampicillin therapy

Conclusion The results suggested that piperacillin therapy has good efficiency and tolerability and that it may be highly effective, even in cases of pneumonia with underlying diseases. This regimen may thus serve as a first line treatment of community-acquired pneumonia.

Key words: community-acquired pneumonia, antibiotics, clinical trials, pulmonary infections

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Introduction

According to the Japanese Ministry of Health, Labor and Welfare (MHLW), pneumonia is the fourth leading cause of death in Japan. When deaths from pneumonia are analyzed by age, elderly patients (aged >65 years) account for >90% of total deaths from pneumonia (1). The high mortality rate among elderly patients with pneumonia is primarily attributable to them being more prone to infection due to compromised immune function caused by underlying disease, malnutrition, etc., and occult misswallowing and reduced drug absorption due to cerebrovascular disease and dementia (2, 3). Since pneumonia in elderly individuals tends to follow a severe course under the influence of these factors, drugs with potent and broad-spectrum antimicrobial activity (e.g., cephalosporins, carbapenems) are often used to manage elderly patients with pneumonia.

In recent years, however, narrow-spectrum antimicrobial agents have been recommended for more widespread use due to their improved medical economics and as a result of bacterial resistance to broad-spectrum antimicrobial agents (4). Under such circumstances, the clinical usefulness of penicillins has been reviewed, and the use of piperacillin

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(PIPC) and ampicillin (ABPC) in combination with beta-lactamase inhibitors is considered to be highly effective.

ABPC is used to treat community-acquired pneumonia, providing cover against streptococcal infection and *Haemophilus influenzae*, and it is recently used together with a beta-lactamase inhibitor to disable or slow down the action of beta-lactamase producing bacteria. But all *Pseudomonas* and most strains of *Klebsiella* are considered resistant against ABPC, whereas PIPC is an extended spectrum beta-lactam antibiotic and has activity against both Gram-positive and Gram-negative pathogens including *Pseudomonas aeruginosa*, which is known as the one of the most important pathogens in hospital-acquired, but not community-acquired pneumonia (CAP) (5, 6).

CAP is an acute infection seen among people participating in ordinary social interactions. The bacterium most frequently isolated from patients with CAP is *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*, but not *Pseudomonas* spp. (5, 7-11). Therefore, it is considered PIPC and ABPC may be usually equal to effective against CAP patients.

Guidelines for the diagnosis and treatment of CAP have been made public in Western countries (5, 9). In Japan, the Japanese Respiratory Society (JRS) proposed guidelines in 2000 (10), with a revision in 2005 (11), and strongly recommended the use of penicillin for mild to moderate CAP patients, however, there is no description of the differences between PIPC and ABPC with a beta-lactamase inhibitor.

This study was undertaken in order to evaluate the usefulness of penicillin, especially PIPC, compared with sulbactam/ampicillin (SBT/ABPC), in the treatment of CAP in adult patients. To this end, the efficacy, safety and cost benefits of PIPC therapy were compared with those of SBT/ABPC therapy.

Materials and Methods

Participating facilities

This study was conducted at the Second Department of Internal Medicine of Nagasaki University Hospital, Nagasaki, and its 12 affiliated facilities between November 2006 and January 2007

Patients

Subjects were diagnosed at the participating facilities as having mild-to-severe bacterial CAP according to the differential criteria of the JRS guidelines (11). The JRS guidelines define CAP as pneumonia present in the general population that not only affects mostly healthy people living ordinary social lives, but also the elderly and those with various underlying diseases. Patients with a history of allergies to PIPC or SBT/ABPC, severely compromised renal or hepatic function, or a successful therapeutic response to previous treatments, as well as those taking steroids (equivalent to > 10 mg/day prednisolone), and those judged by the attending physician to be inappropriate for the study based on immune function or any other reason, including pregnant women were excluded from the study. Prior to the start of the study, the patient or his/her legal agent was informed of the study design and consent was obtained in writing. This trial was approved by the institutional review board of Nagasaki University.

Dose level and administration method

Patients were randomized into two groups using a central web computer-generated system: the PIPC group (treated intravenously with PIPC at 2.0 g twice daily) and the SBT/ABPC group (treated intravenously with SBT/ABPC at 3.0 g twice daily). For each group, treatment was performed for 7 days; however, the administration period was extended (up to day 14), as needed. When fever subsided (<37℃) or other systemic symptoms were alleviated, the attending physician discontinued treatment at his/her discretion. Cases with no signs of improvement after 7 days were rated as non-responders to the therapy.

Treatment was discontinued if any underlying disease or infection was exacerbated, efficacy of treatment was inadequate or the condition was exacerbated, complications were exacerbated, incidental symptoms developed, adverse reactions or laboratory abnormalities developed, the patient or his/her proxy requested discontinuation, or if the attending physician considered discontinuation necessary for other reasons.

Evaluation

Severity of pneumonia was rated based on the attending physician's subjective assessment, in addition to the 2 (previous guideline 2000 and current guideline 2005) JRS classifications of the severity of CAP (10, 11). Subjective and objective symptoms, chest X-ray findings, laboratory test data, and bacteriological test results were evaluated at 3 and 7 days after the start of therapy and after completion.

Bacteriological tests included isolation and identification of bacteria species from sputum and bronchial samples, evaluation of the sensitivity of isolated bacteria to PIPC and SBT/ABPC, urinary pneumococcus antigen test, and observation of bacterial fate and changes in drug sensitivity following treatment. Unfortunately, we did not perform exact detection tests for atypical pathogens, such as *Mycoplasma*, *Chlamydophila*, and *Legionella* spp., however, we used the classification methods to distinguish bacterial/atypical pneumonia recommended by JRS guideline, which sensitivity and specifility were each 77.89/83.86% and 93.01/86.99%, respectively (10, 11). The 6 items for differentiation criteria were as follows: 1. Age below 60 years, 2. Absent of underlying disease, or mild if present, 3. Has persistent cough, 4. No abnormality detected by chest auscultation, 5. No sputum, or no apparent causative bacteria detected by rapid diagnostic test, and 6. Peripheral white blood cell count < 10,000/μL.

The determination as pathogens were dependent on JRS

guidelines and IDSA and/or ATS guidelines (5-7, 10, 11). Diagnosis was usually confirmed by Gram-staining with phagocytosis and collected heavy growth (3+; equal to 1×10^7 cfu/mL of from samples. The probable pathogen was defined by a compatible clinical syndrome with detection (by staining or culture) of a likely pulmonary pathogen in respiratory secretions (expectorated sputum, bronchoscopic aspirate, or quantitatively cultured bronchoscopic bronchoalveolar lavage [BAL] fluid or brush catheter specimen) with semiquantitative culture, which the pathogen should be recovered in moderate (2+) to heavy growth (3+).

Clinical efficacy assessment and analysis

Based on the time course of clinical symptoms from the start of therapy until days 3 and 7 of therapy, the attending physician evaluated the clinical efficacy of the therapy in individual cases using a four-category scale: cured (absence of fever >37.5℃, chill, chest pain, cough and difficulty in breathing), improved (chill and fever absent but symptoms such as chest pain, cough and sputum persist), ineffective and unclassified. Chest X-ray findings were evaluated based on the time course of X-ray findings after the start of therapy using a four-category scale (shadow disappearance, improvement, no change and deterioration). In addition, the committee evaluated clinical efficiency: improved or inefficiency dependent on the endpoints suggested by the Japanese Respiratory Society (JRS) guidelines for the management of community-acquired pneumonia in adults in 2005 (11). The severity of pneumonia was also evaluated by the attending physicians using the JRS Guideline 2000 (10), and JRS Guideline 2005 (11).

Bacteriological efficacy

Bacteriological efficacy was evaluated based on the fate of bacteria after the start of therapy using a five-category scale: disappeared, reduced, replaced by other bacteria, unchanged and unclassified. Bacteriologic responses was categorized into eradication, persisted, and unclassified.

Adverse events (AEs)

For each accompanying symptom or laboratory abnormality appearing during the therapeutic period, the nature, severity, date of onset, treatment provided, and outcome were recorded. Causal relationships to the study drugs were rated as related, possibly related or not related.

Cost benefits

Antibiotic costs related to medical care per pneumonia patient were calculated for each administration period, and compared between the PIPC groups and SBT/ABPC groups.

Statistical analysis

Comparisons between treatment groups were carried out using the most appropriate test from chi-square test, Fisher's-exact test, and student's paired t-test. Additionally, 95% confidence intervals (CI) were calculated for the cure rate and pathogen eradication rate. p values of <0.05 were considered statistically significant.

Results

Subjects

For about 1-year beginning in November 2006, 109 patients were enrolled in this study. All patients were included in a safety evaluation. Seven cases were excluded by the Case Review Committee, and thus a total of 102 patients were included in the efficacy evaluation. Of these, 53 received PIPC therapy and the remaining 49 received SBT/ABPC therapy.

There was no significant difference between the PIPC therapy group and the SBT/ABPC therapy group with regards to background variables such as sex, age, JRS severity rating, underlying disease, complications, past illness, allergy, and period of administration (Table 1).

The most frequent underlying disease was pulmonary disease, which was present in 19 cases of the PIPC group and in 14 cases of the SBT/ABPC group, however, 6/19 cases and 7/14 cases had other underlying diseases without respiratory diseases. Underlying respiratory diseases were bronchial asthma, old tuberculosis, and COPD including pulmonary emphysema and chronic bronchitis. Other underlying diseases and complications included; diabetes mellitus, hypertension, cardiac diseases, and cerebrovascular diseases.

Thirteen of the PIPC patients and 11 of the SBT/ABPC patients were free of underlying disease or complication. With regards to the distribution of each underlying disease or complication, there were no significant differences between the PIPC and SBT/PIPC groups.

Overall clinical efficacy

The total efficacy rate evaluated by the committee was 77.4% (41/53) in the PIPC group and 67.3% (33/49) in the SBT/ABPC group, and did not differ significantly between the two groups (Table 2).

However, we found a significant difference in efficiency between PIPC and SBT/ABPC treatments in male patients (27/34=79.4% vs. 15/27=55.6%, $p<0.046$, respectively), and patients with underlying disease (30/36=83.3% vs. 19/33=57.6%, $p<0.019$, respectively), especially in respiratory disease patients (11/13=84.6% vs. 2/7=28.6%, $p<0.022$, respectively). Furthermore, we found a significant difference in efficiency among SBT/ABPC groups dependent on age.

When analyzed based on the JRS severity rating, using either the previous or current criteria, and with subjective assessment, the efficacy rate in patients with moderate pneumonia did not differ significantly between the PIPC group and SBT/ABPC group. The period of drug administration also showed no significant differences between the PIPC group and SBT/ABPC group.

Table 1. Demographic and Characteristics of the Patients

			PIPC (n = 53)	SBT/ABPC (n = 49)	p-value※
Gender	Male／Female		34／19	27／22	0.352 1)
Mean (±SD) age (years)			71.7±16.3	69.1±17.7	0.436 3)
Severity	A-DROP	Mild	11	13	0.246 2)
		Moderate	41	32	
		Severe	1	4	
	Old GL*	Mild	5	9	0.421 1)
		Moderate	33	28	
		Severe	15	12	
Underlying disease	Yes／No		36／17	33／16	0.950 1)
	(respiratory)		(13)	(7)	
	(respiratory+others)		(6)	(7)	
	(others)		(17)	(19)	
Complications	Yes／No		13／40	15／34	0.492 1)
Past illness	Yes／No		36／17	27／22	0.183 1)
Allergy	Yes／No		3／50	4／45	0.708 2)
Mean (±SD) dosing period (day)			8.25±2.36	8.33±2.93	0.877 3)

* Old version of JRS guideline (2000)
※ 1) χ^2-test 2) Fisher's exact-test 3) t-test (p-value *: p<0.05 **: p<0.01 ***: p<0.001)

Table 2. Clinical Efficiency of PIPC and SBT/ABPC

			PIPC			SBT/ABPC			p-value※
			Efficacy rate (%)		p-value※	Efficacy rate (%)		p-value※	
TOTAL			41／53	77.4	—	33／49	67.3	—	0.258 1)
Gender	Male		27／34	79.4	0.736 2)	15／27	55.6	0.051 1)	0.046* 1)
	Female		14／19	73.7		18／22	81.8		0.709 2)
Age (years)	～49		6／6	100	0.540 2)	6／7	85.7	0.042* 2)	1.000 2)
	50～59		4／5	80.0		6／6	100		0.455 2)
	60～69		2／3	66.7		1／4	25.0		0.486 2)
	70～79		16／20	80.0		12／16	75.0		1.000 2)
	80～89		12／17	70.6		8／15	53.3		0.314 1)
	90～		1／2	50.0		0／1	—		1.000 2)
Severity	A-DROP	Mild	9／11	81.8	1.000 2)	10／13	76.9	0.708 2)	1.000 2)
		Moderate	31／41	75.6		20／32	62.5		0.226 1)
		Severe	1／1	100		3／4	75.0		1.000 2)
	Old GL*	Mild	5／5	100	0.553 2)	8／9	88.9	0.180 2)	1.000 2)
		Moderate	24／33	72.7		19／28	67.9		0.678 1)
		Severe	12／15	80.0		6／12	50.0		0.127 2)
Underlying disease	Yes		30／36	83.3	0.167 2)	19／33	57.6	0.036* 1)	0.019* 1)
	(respiratory)		(11／13)	(84.6)		(2／7)	(28.6)		0.022* 2)
	(respiratory+others)		(4／6)	(66.7)		(4／7)	(57.1)		1.000 2)
	(others)		(15／17)	(88.2)		(13／19)	(68.4)		0.236 2)
	No		11／17	64.7		14／16	87.5		0.225 2)
Dosing period (days)	- 2		0／0	—	0.020* 2)	0／1	0	0.028* 2)	1.000 2)
	3 - 5		2／6	33.3		1／5	20.0		1.000 2)
	6 - 7		9／12	75.0		12／16	75.0		1.000 2)
	8 - 14		30／35	85.7		20／27	74.1		0.250 1)

* Old version of JRS guideline (2000) ※1) χ^2-test 2) Fisher's exact-test 3) t-test (p-value *: p<0.05 **: p<0.01 ***: p<0.001)

Bacteriological efficacy

The most frequent pathogen was *S. pneumoniae* (15 vs. 12 cases, PIPC and SBT/ABPC groups, respectively), followed by *Haemophilus influenzae* (6 vs. 5 cases, PIPC and SBT/ABPC groups, respectively), *K. pneumoniae* (3 vs. 2 cases, PIPC and SBT/ABPC groups, respectively), *M. catarrhalis* (0 vs. 1 case, PIPC and SBT/ABPC groups, respectively), *S. anginosus* (0 vs. 1 case, PIPC and SBT/ABPC groups, respectively), *S. constellatus* (1 vs. 0 case, PIPC and SBT/ABPC groups, respectively), *S. aureus* (methicillin-susceptible *Staphylococcus aureus*; 0 vs. 1 case, PIPC and SBT/ABPC groups, respectively), MRSA (1 vs. 0 case PIPC, and SBT/ABPC groups, respectively), and *E. coli* (0 vs. 2 cases, PIPC and SBT/ABPC groups, respectively), as shown in Table 3.

The eradication rate of *S. pneumoniae* was 100% vs. 90% in PIPC and SBT/ABPC groups, respectively. *H. influenzae* (three frequently isolated strains) was 100% in both the PIPC and SBT/ABPC groups. We did not find significant

Table 3. Bacteriological Efficiency

Causative organisms	PIPC				SBT/ABPC					p-value※
	Total	Eradication	Persisted	Eradication (%)	Total	Eradication	Persisted	Unclassified	Eradication (%)	
S.pneumoniae	15	15		15／15(100)	12	9	1	2	9／10(90)	
S.pneumoniae	13	13		13／13	10	8	1	1	8／9	
PISP	1	1		1／1						
PRSP	1	1		1／1	1	1			1／1	
H.influenzae	6	6		6／6	5	5			5／5	
H.influenzae	5	5		5／5	3	3			3／3	
BLNAS	1	1		1／1						
BLNAR					2	2			2／2	
K.pneumoniae	3	1	2	1／3	2	1		1	1／1	
M.catarrhalis					1	1			1／1	
S.anginosus					1	1			1／1	
S.constellatus	1		1	0／1						
S.aureus					1	1			1／1	
MRSA	1		1	0／1						
E.coli					2	1		1	1／1	
TOTAL	26	22	4	22／26 (84.6)	24	19	1	4	19／20 (95.0)	0.062 2)

Eradication(%)＝Eradicated／(Total－Unevaluable)×100

※ 1) χ^2-test 2) Fisher's exact-test 3) t-test (p-value *:p＜0.05 **:p＜0.01 ***:p＜0.001)

differences due to drug resistance, such as PRSP/PSSP in *S. pneumoniae* and BLNAR/BLNAS in *H. influenzae*, respectively. The overall eradication rate for the pathogenic microorganism was 84.6% (22/26) in the PIPC group and 95.0% (19/20) in the SBT/ABPC group, respectively.

Adverse reactions

In the PIPC group, adverse reactions (adverse events where causal relationship to the drug was not ruled out) were seen in 3 (5.4%) of the 56 patients, with the major adverse reactions being diarrhea and hepatic dysfunction. In the SBT/ABPC group, adverse reactions were seen in 5 (9.4%) of the 53 patients, with the major adverse reactions also being diarrhea and hepatic dysfunction. No significant differences were found between the groups. All reactions were mild or moderate and transient (data not shown).

Cost benefits

Finally, we calculated the antibiotic cost benefit related to medical care for pneumonia patients treated by either PIPC or SBT/ABPC. Although administration periods were relatively similar in the SBT/ABPC and PIPC groups (8.33±2.93 days vs. 8.25±2.36 days, respectively), the patients administered SBT/ABPC had a cost 1.7 times higher than those administered PIPC when vial type products were used (35,271±12,392 yen vs. 13,324±3,815 yen, $p<0.001$, respectively), and 2.6 times higher when bag type products were used (35,454±12,456 yen vs. 21,091±6,039 yen, $p<0.001$). These results suggest a cost benefit for PIPC therapy, compared to SBT/PIPC therapy.

Discussion

Pneumonia is a life-threatening disease, especially in elderly individuals, who have multiple exacerbating factors (susceptibility to further infection, occult mis-swallowing, etc.). Furthermore, the symptoms of pneumonia in elderly patients are often masked by underlying disease. For these reasons, the detection of pneumonia in elderly patients tends to be delayed, often leading to severe bouts of pneumonia (2, 12, 13). Despite the development of various antimicrobial agents, pneumonia continues to have a high mortality rate; therefore, appropriate diagnosis and treatment are essential for pneumonia.

The JRS guidelines (11) strongly recommend a high dose administration of penicillin, including beta-lactamase plus penicillin, for mild to moderate CAP with bacterial pneumonia, especially against pneumonia due to *S. pneumoniae*. However, various kinds of penicillins, especially two types of penicillins, such as ampicillin and piperacillin, have been used in Japan. Okimoto et al (14) reported that the effectiveness of SBT/ABPC therapy for CAP among elderly individuals was 77.1%, while Wood et al (15) conducted a study comparing SBT/ABPC therapy with IPM/CS; carbapenem, one of the most broad spectrum antibiotics, therapy in cases of ventilator-assisted pneumonia caused by *Acinetobacter*, and found that there were no significant inter-group differences in terms of efficacy, mortality rate, duration of mechanical ventilation, duration of ICU stay or duration of hospital stay. On the other hand, a recent study demonstrated that PIPC is more effective even though beta-lactamase inhibitor combined with ampicillin, such as SBT/

ABPC has shown a low efficiency for BLNAR *in vitro* although PIPC has been commercially used for more than twenty years (16). Consequently, it is still unclear which is more beneficial; PIPC or SBT/ABPC administration *in vivo* and in CAP patients.

In this study we demonstrated that PIPC therapy has comparable clinical efficacy to SBT/ABPC therapy in patients with mild-to-severe CAP. The severity of pneumonia was classified based on the criteria of the previous and current JRS guidelines and clinical/bacteriological efficacy was analyzed and compared between the two groups. Unfortunately, we did not assess by PORT classification by IDSA (5, 11) because we could not collect enough data for PORT classification, such as serum glucose sodium, and pH in blood gas, which are not always measured in Japan for CAP patients. Further study will be needed in the near future.

In this analysis, each parameter was comparable between the two groups. Furthermore, the efficacy of PIPC therapy was higher in male patients and those with underlying respiratory diseases, compared with SBT/ABPC therapy. Gender (male) is considered to be one of the important factors in the A-DROP system in new JRS guidelines (11), and respiratory complications are also well known as an influencing factor on severity and prognosis (5-11). These results suggest that PIPC therapy can be expected to exert better efficacy, even in cases of more severe CAP. The reasons that we found higher effectiveness in males and the patients with underlying respiratory diseases might be related to gram-negative bacteria, including *Pseudomonas* spp. and *Haemophilus influenzae*, which were, especially the latter, sometimes difficult to detect by culture from samples. The patients who have underlying diseases, including COPD were known as male dominant and have a high potential to have colonization by gram negative bacterium in their bronchial way (5, 6, 10, 11). Furthermore, it was reported by nationwide surveillance in Japan that PIPC(MIC_{90}: 0.5 μg/mL) was more effective against BLNAR type, compared with SBT/ABPC (MIC_{90}: 8.0 μg/mL, even though both of them showed similar effects against Gram-positive bacteria, including PRSP (17). Some pneumonia cases in this study which pathogens have not detected might be due to potential BLNAR infection.

We found a slightly lower total efficiency in both the PIPC and SBT/ABPC groups, compared with previous penicillin studies on CAP (18-21), however, higher efficiency was found through the attending physician's subjective assessment (94.1% vs. 84.8%, in PIPC and SBT/ABPC groups, respectively: data not shown). This discrepancy is because of protocol errors due to the addition or changing to oral antibiotics by physicians even though the patients tended to improve or recover in most cases. Prompt efficiency will be found if we add the actual effective cases which were counted as ineffective by an adequate administration of oral antibiotics after penicillin therapy (87.2% vs. 76.7%, PIPC and SBT/ABPC cases, respectively; data not shown). A few failure cases in mild patients were found (5 cases): 2 patients in PIPC group and 3 patients in SBT/ABPC group, respectively. These failure cases were as follows: PIPC (case 1; protocol failure by changing antibiotic, and case 2; atypical pneumonia was suspected later), and SBT/ABPC (cases 1 and 3; only 3 days administration, and case 2; protocol failure by changing antibiotic). Short period of antibiotic administration might also be one of the important causes of re-worsening of pneumonia in mild CAP patients. IDSA/ATS guideline also recommended two more days administration of antibiotics after the first assessment for CAP improvement at Day 2 or 3, that means at least 4 or 5 days administration of antibiotics will be needed to prevent re-worsening of CAP patients (5).

For bacteriological efficiency, we found a good eradication rate in both the PIPC and SBT/ABPC groups. PIPC was 100% effective against *S. pneumoniae* and *H. influenzae* cases. We expected PIPC may have been more effective in *H. influenzae* cases, especially BLNAR, but SBT/ABPC were also effective. Further study and patient analysis will be needed.

With regard to safety, no serious adverse reactions were observed in any patients in either the PIPC or SBT/ABPC group, thus suggesting that penicillin therapy is highly tolerable in elderly patients, compared with other types of antibiotics.

It should be noted that although carbapenems exert potent antimicrobial activity against a broad range of bacteria, including Gram-positive and Gram-negative microorganisms, it has been recently reported that metallo-β-lactamase-producing bacteria, which can degrade carbapenems, have become more widespread (4, 22) and that strains of *P. aeruginosa* resistant to carbapenems have been isolated (23). Thus, close attention is now being paid to the spread of drug-resistant bacterial strains caused by the careless and/or excessive use of broad-spectrum antimicrobial agents. Governmental intervention and controls against the use of broad-spectrum drugs and anti-MRSA drugs have also been instituted in recent years. The results of this study suggest that PIPC can be used as an adequate effective antibiotic.

Furthermore, we found a significant antibiotic cost benefit with medical care in the PIPC treatment, compared to the SBT/ABPC treatment. Daily drug costs were as follows: PIPC: SBT/ABPC; 1.616 yen vs. 4.236 yen, respectively for vial type, and 2.558 yen vs. 4.258 yen, respectively for bag type (data not shown). Cost benefit is thought to be one of the more important factors in managing patients with pneumonia, and might influence the medical insurance systems and medical politics in both the United States and Japan (5, 6, 10, 11). These results may also lead to the recommendation of PIPC for CAP treatments.

In conclusion, the present comparison of patients with mild to severe pneumonia has revealed that the clinical efficacy of PIPC is comparable to that of SBT/ABPC, and that PIPC therapy has a cost benefit. PIPC is thus considered to be useful as a first-choice antibiotic in the treatment of CAP even for critical patients, who have underlying respiratory

diseases.

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