INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Multicenter Survey on Hospital-acquired Pneumonia and the Clinical Efficacy of First-line Antibiotics in Japan

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Abstract

Objective The aim of this study was to investigate the pathophysiology of hospital-acquired pneumonia (HAP) and the clinical efficacy of its first-line treatment and to examine the validity of "the Japanese Respiratory Society (JRS) Guidelines for management of HAP".

Methodology The observational survey was conducted during the period of June 2002-May 2004 and patients with HAP were prospectively surveyed using the consecutive enrollment method. A total of 1,356 patients from 254 hospitals nationwide were analyzed. Clinical response to first-line antibiotics was evaluated at the end of the medication.

Results The 30-day mortality rate was 19.8%. Patients were classified into four groups according to the JRS guideline criteria. There were remarkable variances in the number of cases of each group. Mild/moderate pneumonia with no risk factors (group I) accounted for 0.3% of all cases. The mortality rate tended to be higher, as clinical conditions became more serious (group II < III < IV). Alternatively, though categorized in the same group (group III), there was a difference in the mortality rate by the severity of pneumonia (severe cases 32.2% vs. moderate cases 11.0%). First-line medication using carbapenems accounted for 61.7% of total cases. The efficacy rate of guideline-concordant therapy was significantly higher than that of guideline-discordant therapy (54.2% vs. 41.7%).

Conclusions This is the first nationwide study on HAP in Japan. The clinical characteristics and prognosis of HAP were elucidated. Review of the current classification of the disease is required and these results provide valuable information for the next revision of the guidelines.

Key words: antibiotics, guidelines, hospital-acquired pneumonia, surveillance

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Introduction

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection with the highest mortality rate (1). Since it occurs in patients with underlying diseases that undergo a variety of medical treatments, it is highly likely to be caused by resistant bacteria. Since treatment remains difficult and appropriate antibiotics are essential, the establishment of guidelines for standardizing the management of HAP is necessary. The American Thoracic Society (ATS) published guidelines for the management of HAP in 1996 (2) which were then revised as ATS/Infectious Diseases Society of America (IDSA) Joint Guidelines in 2005 (3). In addition, the Japanese Respiratory Society (JRS) published guidelines for HAP in March 2002 (4). Though the ATS/IDSA guideline (3) excludes patients who are known to be immunosuppressed by human immunodeficiency virus infection, hematologic malignancy, chemotherapy-induced neutropenia, organ transplantation, and so on, the JRS guidelines include the case as pneumonia with specific conditions. In the JRS guidelines, the use of an adequate dosage of potent antibiotics with a broad spectrum of action is recommended, when the causative bacteria has not been iso-

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Table 1. Classification of the Severity Rating of Pneumonia (Translated from Japanese Respiratory Society Guidelines)

	Mild	Moderate	Severe
Assessment parameters	Fulfils at least five of the eight criteria	Neither 'mild' nor 'severe'	Fulfils at least five of the eight criteria
Extent of infiltration on the chest X-ray examination	Less than 1/3 area of one lung is infiltrated		More than 2/3 area of one lung is infiltrated
Body temperature	<37.5 ℃		≧38.6 ℃
Pulse rate	<100/min		≧130/min
Respiratory rate	<20/min		≧30/min
Dehydration	(−)	(-) or (+)	(+)
White blood cell counts	<10000/mm^3	Neither 'mild' nor 'severe'	≧20000/mm^3 or <4000/mm^3
C-reactive protein	<10 mg/dl		≧20mg/dl
PaO_2 on room air	>70Torr		≦60Torr SpO_2≦90%

[a] Pneumonia is classified as 'severe', when patients exhibit cyanosis, impaired consciousness, or shock (systolic blood pressure ≦90 mmHg or diastolic blood pressure ≦60 mmHg), or patients require a respirator (FiO_2>35%) to maintain SpO_2>90%, oliguria (urine volume <20 ml/hr or <80 ml per 4 hr) or sepsis, regardless of whether they fulfil the criteria in the table.

lated or identified or if empiric therapy is employed. Following the publication of the JRS guidelines, the validity of the guidelines was examined and reported (5), however, the previous studies dealt with a relatively small number of cases located at a single institution. Therefore, it was considered necessary to examine patients located at several different institutions. This multicenter survey was implemented to investigate the pathophysiology of HAP and the clinical efficacy of its first-line treatment and to examine the validity of the JRS guidelines.

Methods

Subjects

A nationwide prospective observational study was conducted of consecutively enrolled patients with HAP in the period from June 2002 to May 2004 by HAP study group. The investigator registered up to the number of HAP cases that were prescribed in advance. Each patient was registered only once. As this survey was performed under actual clinical conditions, each institution obtained informed consent if necessary. As most of the investigators belong to the clinical division of internal medicine or respirology, this study was mainly focused on HAP in these departments.

Diagnosis and assessment of severity

According to the JRS guideline criteria, patients were diagnosed as having HAP, if the chest X-ray revealed new or progressive infiltration at 48 hours or more after hospitalization and if one or more of the following criteria were fulfilled: (i) symptoms (e.g. fever, chest pain) and laboratory findings (e.g. elevation of C-reactive protein (CRP), erythrocyte sedimentation rate, and leukocyte count) were noted; (ii) relevant organisms were isolated from sputum, blood, transbronchial lavage, transbronchial brushes, and biopsy specimens; (iii) viruses were isolated from bronchial discharge or viral antigens were detected (taking mixed infections into consideration); (iv) serum antibody titres were elevated to a significant extent (taking mixed infections into consideration); (v) pneumonia was proven histopathologically. The severity rating of HAP was assessed (Table 1) and patients were classified according to the guideline criteria (Table 2).

Clinical response

First-line antibiotics were administered within 3 days of HAP diagnosis, and clinical response was evaluated at the

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Table 2. Classification of Patients with Hospital-acquired Pneumonia

Group	Classification
Group I	(A) Patients with mild or moderate pneumonia but without any of the risk factors of pneumonia
Group II	(B) Patients with mild pneumonia and one or more of the risk factors of pneumonia
Group III	(C) Patients with moderate or severe pneumonia and one or more of the risk factors of pneumonia, and patients considered to have severe pneumonia with or without any of the risk factors
Group IV	Patients with a specific pathology
	1 Patients with compromised immunity
	(D) Neutropenia (due to chemotherapy, radiotherapy, leukaemia, or such)
	(E) Cellular immunosuppression (due to organ transplant, long-term steroid therapy, HIV infection, Hodgkin's disease, or such)
	(F) Humoral immunosuppression (due to hypogammaglobulinaemia, multiple myeloma, or such)
	2 (G) Patients on mechanical ventilation
	3 (H) Patients with aspiration pneumonia

Risk factors of pneumonia: conditions that may lead to aspiration of gastric contents; chronic respiratory diseases; heart failure, pulmonary oedema; diabetes, renal failure, chronic liver disease; use of an H_2 blocker or antacid; long-term antibiotic therapy; advanced age of 65 years or more; malignant tumor.

Note: compromised immunity and mechanical ventilation are regarded as specific pathologies (characteristics of Group IV) but not as risk factors.

end of first line medication. As it is more difficult to objectively assess the efficacy of antimicrobial therapy against HAP compared to community-acquired pneumonia (4), the efficacy of HAP therapy was evaluated on the basis of overall improvement using 5 grades: (i) improved; (ii) slightly improved; (iii) unchanged; (iv) aggravated; (v) non-evaluable. The efficacy rate was calculated defining "improved" cases as effective. The bacterial eradication rate was evaluated in a group of patients in whom causative organisms were presumed by the bacteriological test. When the presumed causative organisms were eliminated at the end of first line medication, the bacteriological response was defined as eradicated. Susceptibility data of the presumed causative organisms to meropenem, a widely used carbapenem in Japan, was collected if the susceptibility test was performed.

Prognosis

The prognosis was evaluated 30 days after initiation of the first-line medication and the survival rate was estimated.

Statistical analysis

In case of a two-by-two contingency table, data were analyzed using Fisher's exact test. Where necessary, data were also analyzed using the Cochran-Armitage test. In the investigation of factors affecting efficacy or prognosis, data were analyzed with multiple logistic regression analysis. A risk rate of less than 5% was regarded as significant. All analyses were performed by SAS software version 8.2 (SAS Institute).

Results

Case composition

From a total of 254 institutions, 1,478 patients were enrolled and case cards of 1,460 patients were collected. Out of the 1,460 cases collected, 1,356, 1,351 and 1,316 patient profiles, prognosis and efficacy cases were analyzed, respectively (Fig. 1).

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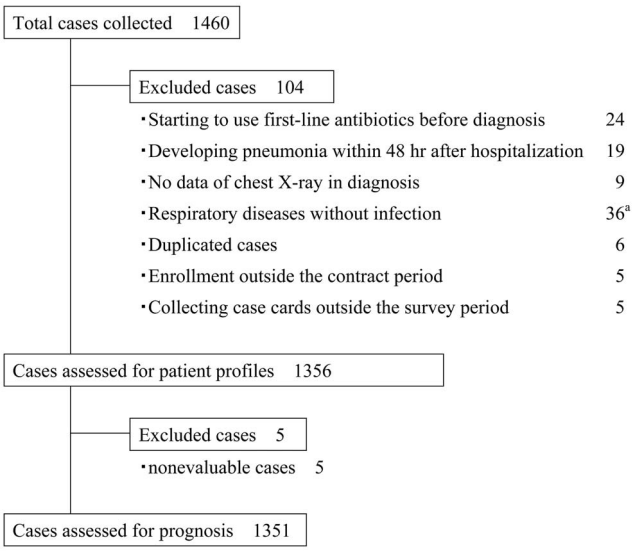

[a] lung cancer (13), interstitial pneumonia (8), pulmonary emphysema (5), chronic respiratory failure (2), etc.

Figure 1. **Case breakdown**

Table 3. **Patient Characteristics**

Item	Category		Cases (%)
Gender	Male		939 (69.2%)
	Female		417 (30.8%)
Age (years)	＜65		258 (19.0%)
	65≦＜80		652 (48.1%)
	80≦		446 (32.9%)
Onset time	2≦＜5		125 (9.2%)
(days)	5≦≦30		571 (42.1%)
	30＜		660 (48.7%)
Severity	Mild		183 (13.5%)
	Moderate		617 (45.5%)
	Severe		556 (41.0%)
Risk factors	No		12 (0.9%)
	Yes		1344 (99.1%)
Disease type	Group I	(A)	4 (0.3%)
	Group II	(B)	115 (8.5%)
	Group III	(C)	592 (43.7%)
	Group IV [a]		645 (47.6%)
		D	151 (11.1%)
		E	139 (10.3%)
		F	20 (1.5%)
		G	90 (6.6%)
		H	332 (24.5%)

[a] Including cases with plural types (D～H) of pneumonia

Patient characteristics

Cases in hospitals with more than 300 beds accounted for 78.1% (1,059 cases) of the total. Regarding clinical division, internal medicine and respiratory disease accounted for 91.2% (1,236 cases). There were 13 cases (1.0%) reported from intensive care units (ICU).

Cases with an onset of less than 5 days after hospitalization, i.e. early onset cases, accounted for 9.2% (125 cases) of all cases (Table 3). In contrast, cases with an onset of more than 30 days after hospitalization accounted for 48.7% (660 cases). About ventilator associated pneumonia (VAP) cases, early onset cases accounted for 22.2% (20 cases). In addition, since elderly patients of 65 years or older accounted for 81.0% (1,098 cases) of the total, risk factors designated by the JRS guideline were found in most cases (99.1%: 1,344 cases).

The laboratory tests used for severity rating designated by the JRS guideline consisted of body temperature, pulse rate, dehydration, white blood cell counts and CRP and were all evaluated at diagnosis in more than 95% of patients. Alternatively, respiratory rate and PaO_2 were determined in 55.4% (751 cases) and 34.9% (473 cases) of the total, respectively.

As for disease types, pneumonia with specific conditions (group IV), moderate pneumonia with risk factors, or severe pneumonia (group III) accounted for 91.2% (1,237 cases) of all cases (Table 3). In contrast, mild/moderate pneumonia with no risk factors present (group I), VAP (type G) and pneumonia with humoral immunodeficiency (type F) accounted for 0.3% (4 cases), 6.6% (90 cases) and 1.5% (20 cases) of the total, respectively. In addition, 77 patients (5.7%) corresponded to plural disease types in group IV.

While unimodal distribution peaked at an age of 75-79

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Table 4. Details of Causative Organisms

Causative organism presumed	Cases (n=816)	Current hospitalization (days)			
		2≦＜5 (n=71)	5≦≦30 (n=329)	30＜ (n=416)	p-value [a]
Staphylococcus aureus [b]	25.5%(208)	16(22.5%)	99(30.1%)	93(22.4%)	N.S.(p=0.091)
MSSA [c]	4.3%(35)	5(7.0%)	15(4.6%)	15(3.6%)	N.S.(p=0.235)
MRSA [d]	17.3%(141)	6(8.5%)	71(21.6%)	64(15.4%)	N.S.(p=0.460)
Pseudomonas aeruginosa	18.3%(149)	9(12.7%)	47(14.3%)	93(22.4%)	p=0.002
Klebsiella pneumoniae	8.2% (67)	5(7.0%)	26(7.9%)	36(8.7%)	N.S.(p=0.606)
Streptococcus pneumoniae	5.0%(41)	5(7.0%)	21(6.4%)	15(3.6%)	N.S.(p=0.059)
Candida species	4.4%(36)	8(11.3%)	10(3.0%)	18(4.3%)	N.S.(p=0.372)
Haemophilus influenzae	3.6%(29)	3(4.2%)	13(4.0%)	13(3.1%)	N.S.(p=0.496)
Serratia marcescens	2.9%(24)	2(2.8%)	10(3.0%)	12(2.9%)	N.S.(p=0.945)
Others	32.1%(262)	23(32.4%)	103(31.3%)	136(32.7%)	N.S.(p=0.758)

[a] Cochran-Armitage analysis

[b] Including MSSA and MRSA

[c] Methicillin-susceptible *Staphylococcus aureus*

[d] Methicillin-resistant *Staphylococcus aureus*

years and declined sharply after 80 years of age in men, bimodal distribution peaked at 50-59 years and another peak observed at 75-79 years of age was observed in women and in several patients of 80 years and older. The complication rate with malignant tumors was higher in younger patients than in elderly patients. Adversely, aspiration pneumonia (type H) increased proportionally to age.

Presumed causative organisms

Bacteriological tests, prior to initiating first-line therapy, were performed in 832 patients (61.4%) and the causative organisms could be presumed by physician in charge in 567 (41.8%) of these patients. Out of the 567 cases, 34.0% were due to polymicrobial infection. The causative organisms were presumed by the bacteriological test data from mainly sputum samples (91.5%: 747/816), followed in descending order by blood (3.8%: 31/816) and others such as bronchoalveolar lavage (4.7%: 38/816). The most common pathogens were *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]) (25.5%), followed by *Pseudomonas aeruginosa* (18.3%), *Klebsiella pneumoniae* (8.2%) (Table 4). The isolation frequency of *Acinetobacter* spp. was 0.7%. Additionally, *P. aeruginosa* was more frequent in proportion to the number of days from hospitalization to onset.

Clinical efficacy/prognosis

The efficacy rate of first-line medication was 51.1% (673/1,316). The most common reason for "unchanged" or "aggravated" cases was due to the "effects of underlying diseases," which accounted for 71.5% (253/354).

The 30 day mortality rate was 19.8% (268/1,351). The causes of death included HAP, which accounted for 34.7% (93 cases) of all cases, and underlying diseases, which accounted for 62.7% (168 cases). The breakdown of "survival" cases were "treatment completed" in 845 (78.0%) patients and "treatment ongoing" in 203 (18.7%) patients.

The efficacy and mortality rate by disease type tended to be higher as clinical conditions became more severe (group II < III < IV) (Table 5). Group III pneumonia consists of "moderate cases with risk factors" and "severe cases", and the efficacy and mortality rate in "severe cases" were higher than those in "moderate cases with risk factors".

Details of first-line medication

Main first-line antibiotics used were as follows; carbapenems (61.7%: 837 cases), anti-pseudomonal cephems (17.3%: 235 cases), and clindamycin (9.3%: 126 cases). Carbapenems tended to be used in severe cases and the efficacy rate of carbapenem therapy (53.6%: 435/812) was higher than that of the other antibiotic therapy (47.2%: 238/504) (p=0.027; Fisher analysis). The use of glycopeptides and intravenous fluoroquinolones accounted for 3.8% (51 and 52 cases, respectively) of total cases. Monotherapy using carbapenems accounted for 45.1% (612 cases) of total cases and its efficacy rate was 55.6% (330/593) (Table 6).

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Table 5. Clinical Efficacy and Prognosis by Disease Type

Item	Category	Efficacy (%)	p-value	Mortality rate (%)	p-value
Disease type	Group I (A)	100% (4/ 4)		− (0/ 4)	
	Group II (B)	59.8% (67/112)	p<0.001[a]	9.6% (11/115)	p=0.003[a]
	Group III (C)	55.8% (319/572)		19.2% (113/590)	
	Group IV	45.1% (283/628)		22.4% (144/642)	
	D	49.3% (71/144)		19.9% (30/151)	
	E	45.1% (60/133)		32.4% (45/139)	
	F	42.1% (8/ 19)		40.0% (8/ 20)	
	G	31.5% (28/ 89)		27.8% (25/ 90)	
	H	44.8% (146/326)		19.1% (63/329)	
GroupⅢ (C)	Moderate pneumonia with a risk factor	61.2% (218/356)	p=0.001[b]	11.0% (40/363)	p<0.001[b]
	Severe pneumonia	46.8% (101/216)		32.2% (73/227)	

[a] Cochran-Armitage analysis, [b] Fisher analysis

Table 6. Details of Clinical Efficacy of First-line Medication

First-line medication	Cases (%)	Efficacy(%)	ratio of severe cases
Monotherapy			
Carbapenems	612 (45.1%)	55.6% (330/593)	41.0%
Fourth-generation cephems	101 (7.4%)	54.5% (55/101)	27.7%
Penicillins combined with a β–lactamase inhibitor	60 (4.4%)	43.1% (25/ 58)	35.0%
Third-generation cephems having activity against *Pseudomonas aeruginosa*	42 (3.1%)	42.1% (16/ 38)	35.7%
Intravenous fluoroquinolones	18 (1.3%)	50.0% (9/ 18)	33.3%
Glycopeptides	12 (0.9%)	27.3% (3/ 11)	66.7%
Others	152 (11.2%)	48.3% (71/147)	24.3%
Combination therapy			
Carbapenems + Others	225 (16.6%)	47.9% (105/219)	54.2%
Other combinations	134 (9.9%)	45.0% (59/131)	50.7%

Daily dosage of main first-line antibiotics

The maximum daily dosage of main first-line antibiotics for cases of severe pneumonia is shown in Table 7. Carbapenems and anti-pseudomonal cephems were administered at usual daily doses approved in Japan (meropenem, imipenem 0.5-1 g, panipenem 1 g, biapenem 0.6 g, anti-pseudomonal cephems 1-2 g) in more than 90% of severe cases.

Clinical efficacy against main causative organisms

In the cases with MRSA pneumonia, both the bacterial eradication rate (9.5%: 6/63) and efficacy rate (33.8%: 46/136) remained low and mortality rate also tended to be lower (33.6%: 46/137).

In contrast, in cases with *P. aeruginosa* pneumonia excluding polymicrobial *S. aureus* infection cases, the bacterial eradication, efficacy and mortarity rate were 31.9% (15/47), 52.3% (58/111) and 22.8% (26/114), respectively. As for

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Table 7. Details of Maximum Daily Dose of First-line Antibiotics against Severe Pneumonia

First-line antibiotics	Maximum daily dose	Cases (%)
Carbapenems	＜Approved usual dose [a]	1.9% (7/377)
	Approved usual dose	90.2% (340/377)
	Approved usual dose＜	8.0% (30/377)
Anti-pseudomonal cephems	＜Approved usual dose [b]	1.1% (1/ 88)
	Approved usual dose	90.9% (80/ 88)
	Approved usual dose＜	8.0% (7/ 88)

[a] Meropenem, imipenem 0.5-1 g, panipenem 1g, biapenem 0.6 g

[b] Cefepime, cefozopran, cefpirome, ceftadizime, cefoperazone, sulbactam/cefoperazone 1-2 g

Table 8. Factors Significantly Associated with Clinical Efficacy of First-line Antibiotics in the Multiple Logistic Regression Analysis[a]

Variable	Odd ratio (95%CI)	p-value
Malignant tumor (present)	0.501 (0.385-0.652)	<0.0001
Extent of infiltration on the chest X-ray examination (mild/moderate/severe)	0.668 (0.570-0.783)	<0.0001
Long-term antibiotic therapy (present)	0.406 (0.265-0.622)	<0.0001
States requiring a respirator (present)	0.387 (0.243-0.616)	<0.0001
Aspiration (present)	0.600 (0.436-0.826)	0.0017
Carbapenems (used)	1.458 (1.141-1.863)	0.0026
Dehydration (mild/moderate/severe)	0.792 (0.671-0.936)	0.0062
Oliguria (present)	0.378 (0.160-0.891)	0.0261
Chronic respiratory diseases (present)	1.332 (1.003-1.768)	0.0478

[a] Stepwise method, $p<0.1$ (n=1245)

Variables used are as follows : Gender, Extent of infiltration on the chest X-ray examination, Body temperature, Respiratory rate, Dehydration, White blood cell counts, C-reactive protein, severe states, risk factors, and specific condition defined in the Japanese Respiratory Society guidelines, Current hospitalization, Age, First-line antibiotic (Carbapenems, Fourth-generation cephems etc)

susceptibility of *P. aeruginosa* isolates, the minimum inhibitory concentration (MIC)-range, MIC_{50} and MIC_{90} of meropenem against 32 strains were 0.13-16 μg/ml, 2 μg/ml, and 8 μg/ml, respectively. In addition, the susceptibility rate to meropenem designated by the disk method (KB disk, Eiken Chemical Co., Ltd., Tokyo, Japan) was 81.3% (33/40). The efficacy rate of carbapenem therapy for *P. aeruginosa* pneumonia excluding polymicrobial *S. aureus* infection cases was 61.4% (43/70), which was higher than that of the other antibiotic therapy (36.2%: 17/47).

Analysis of factors affecting efficacy rate/prognosis

Results obtained from multiple logistic regression analysis showed that factors such as complications of malignant tumors had negative effects on the efficacy rate (Table 8). The use of carbapenems as first line treatment had a positive effect on the efficacy rate. As for prognosis, similar significant influences were observed in factors such as malignant tumor, impaired consciousness, cellular immunosuppression, gender, body temperature, CRP, and oliguria (Table 9). In

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Table 9. Factors Significantly Associated with Prognosis in the Multiple Logistic Regression Analysis[a]

Variable	Odd ratio (95%CI)	p-value
Malignant tumor (present)	3.555 (2.497-5.061)	<0.0001
Impaired consciousness (present)	2.406 (1.667-3.472)	<0.0001
Cellular immunosuppression (present)	2.035 (1.309-3.165)	0.0016
Gender (female/male)	1.748 (1.214-2.519)	0.0027
Body temperature (mild/moderate/severe)	0.731 (0.589-0.908)	0.0046
C-reactive protein (mild/moderate/severe)	1.322 (1.072-1.630)	0.0091
Oliguria (present)	2.863 (1.286-6.376)	0.0100
Extent of infiltration on the chest X-ray examination (mild/moderate/severe)	1.285 (1.051-1.572)	0.0147
Requiring FiO_2>35% to maintain SpO_2>90% (present)	1.567 (1.071-2.291)	0.0206
Neutropenia (present)	0.553 (0.332-0.922)	0.0231
Aminoglycosides (used)	2.189 (1.057-4.533)	0.0349
Current hospitalization (-4days/5-30days/31days-)	1.296 (1.009-1.665)	0.0425

[a] Stepwise method, p<0.1 (n=1279)

Variables used are as follows : Gender, Extent of infiltration on the chest X-ray examination, Body temperature, Respiratory rate, Dehydration, White blood cell counts, C-reactive protein, severe states, risk factors, and specific condition defined in the Japanese Respiratory Society guidelines, Current hospitalization, Age, First-line antibiotic (Carbapenems, Fourth-generation cephems etc).

relation to body temperature, the survival rate was lowest in mild cases (≤37.5℃).

Discussion

Multicenter study on HAP in Japan was performed. In this article, patient profiles and prognosis of HAP from 254 institutions were mainly analyzed. The pathophysiology of HAP varies at different medical institutions; for example, its morbidity and mortality are thought to be higher in larger hospitals than in small hospitals (2). This study mainly involved patients in larger hospitals. With regard to HAP prognosis, the mortality rate that is usually reported is 20-50% (1), 50-60% for ICU admissions (6), and 70% in the case of VAP (7). The mortality rate in this study (20%) appeared to be influenced by the fact that there were fewer ICU cases and that the differences in the medical insurance system between the U.S. and Japan resulted in many immunocompetent cases of long-term hospitalization in Japan.

The ATS/IDSA guidelines on HAP define onset in less than 5 days after hospitalization as early onset, and onset after 5 days as late onset (2, 3). Results from this study showed that early onset cases accounted for less than 10% of cases. Therefore, when using the algorism of the ATS/IDSA guidelines (3), most of the cases studied were categorized into the group needing intensive combination antibiotic treatment as empiric therapy. Considering the relatively low mortality rate of HAP in Japan, it is considered to be inappropriate to apply the ATS/IDSA guidelines (3) to HAP of Japan. In the U.S., a number of studies were performed on VAP (8). There were few cases of VAP in this study, partly because fewer cases were collected from the ICU. In addition, the ratio of aspiration pneumonia was higher in elderly patients. It is generally accepted that aspiration pneumonia, due to inapparent aspiration associated with reduction in swallowing reflex and cough reflex, increases in elderly patients and results of this study appear to confirm these findings.

As for classification by disease type in the JRS guidelines, it is a problem that the 30 day mortality rate significantly varied with severity in the group III pneumonia. Of the pneumonia with specific pathology (group IV), the mortality rate of type E and type F pneumonia was relatively high. As more than 70% of their cause of death is underlying disease, the high mortality rate was considered to be due to the severe clinical condition. Furthermore, clearer status

should be given to cases with plural type group IV pneumonia.

Among the laboratory tests used for estimating severity rating in the JRS guidelines, respiratory rate and PaO_2 were determined in less than 60% of cases. Therefore, these laboratory data was considered not to be suitable for the severity rating item in the guideline. The criteria for severity rating in the JRS guidelines were settled on the basis of methods (9), which were made for the efficacy evaluation of trial drugs. Considering that prognosis of patients with pneumonia was the primary end-point, the setting of criteria such as CURB-65 (10) and A-DROP (11) in CAP was more appropriate and the review on severity estimation is considered necessary in the next guideline revision. Regarding body temperature, the mortality rate appeared higher in patients with a low-grade temperature on diagnosis. Riquelme et al reported that both incidence and severity of fever were generally lower in elderly patients with pneumonia and prognosis was poorer in patients with a low temperature (12). Results from this study almost corresponded with these previous findings and the categories of severity for body temperature at diagnosis necessitate a review.

The JRS guidelines recommend the implementation of a bacteriological test; however, this study has shown that the test before first-line treatment was performed in 61.4% of total cases. The ATS/IDSA guidelines on HAP (3) emphasize that the bacteriological test should be performed in combination with initial potent antibiotics, and 2-3 days later, de-escalation of antibiotics should be performed on the basis of the results from the bacteriological test and clinical response (3). In countries such as the U.S., as most reported HAP were VAP cases, causative organisms can be determined with high probability. In contrast, as most HAP in Japan were non-VAP cases with diverse backgrounds and severity, the ratio of the causative organism identified coses was low and de-escalation of antibiotics on the basis of bacteriological test results could not be easily performed. However, as it is important to promote a de-escalation strategy in terms of efficient use of medical resources, the strategy should be recommended by definitively demonstrating applicable cases and necessary clinical conditions for de-escalation. We expect the next revision of the guidelines to play an important role in this endeavor. Microbiological etiology in this study almost corresponded with previous reports from various investigators (13-15). Therefore, collected data about presumed causative organisms in this study appeared to be feasible and to reflect the actual conditions of HAP. The frequency of *P. aeruginosa* was significantly higher in proportion to the number of days from hospitalization to onset. It is generally accepted that the isolation frequency of gram-negative rods with decreased susceptibility to antibiotics becomes higher as the duration of hospitalization is prolonged. Results from this study appeared to correspond with these findings. In addition, the isolation frequency of *Acinetobacter* spp., which was considered one of the major causative organisms of HAP (16), was low and this appeared to be due to the fact that VAP cases were few in this study.

The efficacy rate of guideline-concordant therapy (54.2%: 537/990) was significantly higher than that of guideline-discordant therapy (41.7%: 136/326). This appeared to reconfirm the validity of the guidelines, and the importance of the initial use of potent antibiotics with a broad spectrum range. The use of carbapenems as first-line treatment accounted for 61.7% of total cases, which was in accordance with recommendations in the JRS guidelines and was considered a valid result. Carbapenems were used preferably for severe cases, and the efficacy rate in carbapenem-treated cases was higher than that in carbapenem-untreated cases as reported by Ohi et al (5). It was confirmed that carbapenems played a pivotal role in first-line treatment of HAP. As intravenous fluoroquinolones were reported to retain activity against respiratory isolates of *P. aeruginosa* in Japan (17), the JRS guidelines recommend the use of intravenous fluoroquinolone as well as carbapenems for first-line treatment. However, the ratio of use of these agents in this study was as low as 3.8%. This result appears to be responsible for the restriction on their use in first-line treatment at the dosage and administration, which existed before 2006 in Japan. Furthermore, despite the large proportion of MRSA as causative organism, the ratio of use of glycopeptides in this study was also low. Considering that both the clinical effect and prognosis were poor in cases of MRSA pneumonia, first-line treatment in combination with anti-MRSA agents appeared to be necessary for cases with a risk of MRSA. In cases with *P. aeruginosa* infection, there were also some cases in which the causative organisms persisted even though clinical efficacy was evident. These results appear to be responsible for the fact that, in these cases, biofilm formation of *P. aeruginosa* prevented complete eradication of organisms inside the biofilm (18). In addition, the ATS/IDSA guidelines on HAP established the dosage of antibiotics on the basis of the policy to conduct treatment with high doses of potent agents from an early stage (3). In contrast, the JRS guidelines do not specify dosage of antibiotics required. Since the study demonstrates that the usual dosages, which were less than the approved maximum dosage, were used in most of severe cases, it is necessary to mention the importance of establishing dosage schedule based on the pharmacokinetics/pharmacodynamics theory on the next occasion of guideline revision. The optimization of dosage schedule may bring about an improvement of the current efficacy rate of first-line therapy.

Through this first nationwide study on HAP in Japan, we could understand the pathogenesis, clinical efficacy of first-line antibiotics, and factors affecting efficacy rate and prognosis of HAP in Japan. We believe that the findings obtained from this survey provide valuable information for the recommendation of proper guidelines on HAP.

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