Characteristics and Disease Severity of Healthcare-Associated Pneumonia among Patients in a Hospital in Kitakyusyu, Japan

Masafumi Seki*[1-3], Kohji Hashiguchi[1-4], Akitaka Tanaka[1-3], Kosuke Kosai[1-3], Tomoyuki Kakugawa[1-3], Kazuyuki Awaya[3], Shintaro Kurihara[2], Koichi Izumikawa[1,2], Hiroshi Kakeya[1,2], Yoshihiro Yamamoto[1,2], Katsunori Yanagihara[2], Takayoshi Tashiro[2] and Shigeru Kohno[1,2]

[1]Department of Molecular Microbiology and Immunology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan. [2]Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan. [3]Kitakyushu City Yahata Hospital, Kitakyusyu City, Fukuoka, [4]Nagasaki Atomic Bomb Hospital, Nagasaki, Japan.

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*Correspondence: Masafumi Seki MD, PhD, Second Department of Internal Medicine,

Tel: +81-95-849-7273, Fax: +81-95-849-7285, E-mail: seki@nagasaki-u.ac.jp

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ABSTRACT

Healthcare–associated pneumonia (HCAP) is a newly identified condition and epidemiologic studies in Japan are still limited. We retrospectively observed patients with HCAP and community-acquired pneumonia (CAP) who were hospitalized between December 2004 and March 2005, and compared their disease characteristics. A total of 34 patients (14 with HCAP and 20 with CAP) were evaluated. Of the patients with HCAP, seven (50%) were hospitalized for at least 2 days in the preceding 90 days and five (35.7%) resided in a nursing home or extended care facility. Compared with patients with CAP, patients with HCAP were older, had more complications, including central nerve diseases, had greater disease severity, but lower serum albumin level. More methicillin-resistant *Staphylococcus aureus*, Pseudomonas spp. and anaerobes were isolated from patients with HCAP than from those with CAP. Conversely, more *Streptococcus pneumoniae* was detected and more penicillin was used in patients with CAP. This study provides additional evidence that HCAP should be distinguished from CAP and suggests the pathogenesis and therapeutic strategy for HCAP may be similar to those of hospital-acquired pneumonia (HAP).

Key Words

aspiration pneumonia, albumin, anaerobes, A-DROP, pneumonia severity index, I-ROAD

Abbreviations: A-DROP: age, dehydration, respiratory failure, orientation disturbance, low blood pressure; ATS: American Thoracic Society; CAP: community-acquired pneumonia; CI :confidence interval; ESBL: extended-spectrum β-lactamase; HAP: hospital-acquired pneumonia; HCAP: healthcare–associated pneumonia; IDSA: Infectious Diseases Society of America; I-ROAD: immunodeficiency, age, respiratory failure, orientation disturbance, dehydration; MDR: multidrug-resistant; MRSA: methicillin-resistant *Staphylococcus aureus*; NHAP: nursing home-acquired pneumonia; PDR: potentially drug-resistant

INTRODUCTION

Healthcare–associated pneumonia (HCAP) is a newly identified condition and has been documented in the 2005 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines [1]. Previously, the cases of HCAP substantially overlapped with those of community-acquired pneumonia (CAP); however, HCAP is distinct from CAP because the epidemiologic pattern of HCAP is similar to that of hospital–acquired pneumonia (HAP), which has risk factors for multidrug-resistant (MDR) pathogens [2-3].

Kollef *et al*. analyzed 4,543 patients with culture-positive pneumonia admitted into 59 US hospitals and found that approximately one-half of hospitalized patients with pneumonia had CAP and >20% had HCAP. They reported that the mortality rates associated with HCAP (19.8%) and HAP (18.8%) were comparable ($p > 0.05$) and both were significantly higher than that for CAP (10%, all $p < 0.0001$) and lower than that for ventilator–associated pneumonia (29.3%, all $p < 0.0001$) [4].

Micek *et al*. also analyzed 639 patients in the United States and reported that HCAP was more common than CAP (67.4% versus 32.6%) and that the hospital mortality rate was statistically greater among patients with HCAP than with CAP (24.6% versus 9.1%; $P <$

0.001) [5]. These studies recommended early and appropriate administration of antibiotics similar to the strategy for patients with HAP.

In contrast, the British Thoracic Society guidelines have documented that patients with nursing home–acquired pneumonia (NHAP), which is usually categorized with HCAP, should be treated as having CAP because there is no difference in the distribution of causative pathogens between patients with NHAP and other older adults with CAP[6-7]; this is similar to other recent studies regarding NHAP and pneumonia in residents of long-term care facilities [8-9]. These studies suggested that the pathogenesis of HCAP is heterogeneous and further evidence is required to clarify the differences among HCAP, CAP, and HAP.

The objective of this study was to determine the differences in baseline characteristics between patients with HCAP and CAP in Japan and to clarify the strategy for the treatment of HCAP. In particular, we focused on patient background, disease severity, and specific characteristics, including physical examination and laboratory data, of patients with HCAP.

MATERIALS and METHODS

Study design and patient population

We conducted a retrospective observational study of patients with pneumonia hospitalized at Kitakyusyu City Yahata Hospital (a 300-bed community hospital in Kitakyusyu City, Fukuoka, Japan) between December 1, 2004 and March 30, 2005. Patients with HAP were excluded. We categorized the study patients into HCAP or CAP groups and compared baseline characteristics, disease severity, pathogen distribution, antibiotic regimens, and clinical outcomes between the pneumonia groups. We adhered to the Japanese ethical guidelines for epidemiologic studies and the protocol of this study was approved by the ethics committees of Kitakyushu City Yahata Hospital and Nagasaki University.

Definitions

HCAP and CAP were defined according to the ATS/IDSA guidelines [1-3]. HCAP was determined in patients with any of the following: (1) hospitalization for ≥2 days in the preceding 90 days; (2) residence in a nursing home or extended care facility; (3) home infusion therapy (including antibiotics); (4) long-term dialysis (including hemodialysis and

peritoneal dialysis) within 30 days of entering the study; or (5) home wound care. Complications were defined as described previously by Seki *et al.* [10-11] and Shindo *et al.* [12].

Microbiological evaluation

Pathogens in samples obtained from respiratory tracts, blood, and other samples were investigated. These samples were cultured in sheep blood agar, chocolate agar, and potato dextrose agar in a semiquantitative manner. Positive bacterial culture results for respiratory tracts, other than for the normal flora, are described in the table of microbial identification. Serologic methods using single or paired sera were used to detect antibodies against *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. Influenza virus antigen in nasopharyngeal swabs and *Legionella pneumophila* serogroup 1 antigen in urine samples were detected by immunochromatography.

Disease severity evaluation

Pneumonia severity was assessed by a clinical severity scale, the Pneumonia Severity Index (PSI), published by IDSA, which was calculated from data regarding age,

complications, physical examination findings, and laboratory data on admission [2, 13]. Chest X-ray findings were reviewed and assessed by three physicians blindly and the levels of infiltrates were determined.

The severity of pneumonia was also evaluated using the predictive rules for CAP and HAP in Japan proposed by the Japanese Respiratory Society: the A-DROP (age, dehydration, respiratory failure, orientation disturbance, and low blood pressure)[14] and the I-ROAD (immunodeficiency, age, respiratory failure, orientation disturbance, and dehydration)[11, 15] 5-point scoring system, respectively. Those are modified versions of the CURB-65 (confusion, blood urea nitrogen >20 mg/dL, respiratory rate >30 breaths/min, systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg, and age >65 years) clinical prediction rule[2, 6].

Statistical analysis

A statistical software package (SPSS for Windows, version 16.0J; SPSS Inc., Chicago, IL) was used for all statistical comparisons. Comparisons between groups were carried out using the most appropriate test from the chi-square test, the Wilcoxon test for continuous variables, Fisher's-exact test, and student's paired t-test. Additionally, relative coefficients by

Pearson's and Spearman's rank correlation tests were calculated for the mortality rate. P values of <0.05 were considered statistically significant.

RESULTS

Patients

A total of 34 patients were evaluated during the study period, comprising 14 patients with HCAP (41.2%) and 20 patients with CAP (58.8%). Of the patients with HCAP, seven (50%) had been hospitalized for at least 2 days in the preceding 90 days and five (35.7%) resided in a nursing home or extended care facility. Two (14.7%) were receiving home infusion therapy (including antibiotics). There were no patients who had a background of long-term dialysis within 30 days and home wound care (data not shown).

Patients with HCAP were significantly older than those with CAP, but the male/female ratio did not differ substantially between the two groups (Table 1). In addition, all 14 of the patients with HCAP (100%) had complications, in contrast to only 14 (75%) of the patients with CAP. Among complications, central nerve diseases were significantly found in patients with HCAP compared to those with CAP. The incidences of chronic lung diseases, including old tuberculosis, bronchial asthma, COPD, and idiopathic pulmonary fibrosis, chronic heart diseases, neoplastic diseases, collagen diseases, liver disease, and diabetes were similar between the two groups.

Physical examinations and laboratory data

Fever was the most common physical finding, but the average temperature was not higher in patients with HCAP than in those with CAP (Table 2). Heart rate, respiratory rate, and the number of dehydrated and disoriented patients were the same between the two groups.

The laboratory findings, including white blood cell count and C-reactive protein level, were nearly similar between the two groups. The saturation of peripheral oxygen (SpO_2) level was not different between the two groups. However, serum albumin levels were significantly lower in patients with HCAP compared to those with CAP.

Chest infiltrates comprised the most common radiographic abnormality in patients with HCAP. The percentage of patients who had severe levels of infiltrates, occupying over two-thirds of the lateral lung field, was significantly higher in patients with HCAP (21.4%) than in patients with CAP (5.0%). In contrast, the percentage of patients who had mild levels, less than one-third of the lateral lung field occupied by infiltrates, was significant lower in patients with HCAP (42.6%), compared to patients with CAP (85.0%).

Disease severity

The severity of HCAP was assessed by the criteria of the PSI of IDSA, A-DROP, and I-ROAD of the Japanese Respiratory Society, respectively (Table 2). The PSI of patients with HCAP was significantly higher than that of patients with CAP. However, the A-DROP score of patients with HCAP was relatively similar to that of patients with CAP. In contrast, the I-ROAD score of patients with HCAP was significantly higher than that of patients with CAP.

Pathogen distribution

The microbes identified in the HCAP and CAP groups are shown in Table 3. MRSA and anaerobes were detected more frequently in patients with HCAP than in patients with CAP. Conversely, *Streptococcus pneumoniae* was more frequently isolated from patients with CAP. In addition, the isolation rates of Gram-negative pathogens were the same between the two groups; however, Pseudomonas species, which have potential antibiotic resistance, were isolated significantly from patients with HCAP, but not from those with CAP.

Antibiotic treatment and clinical outcomes

Table 4 shows the initial antibiotic treatments of patients with HCAP and CAP.

Patients with HCAP generally received antibiotic monotherapy, especially with carbapenems and quinolones as the initial treatment. Among the antibiotics, penicillin was used statistical less frequently in patients with HCAP compared to those with CAP.

Combination therapy was also generally used in patients with HCAP. Anti-MRSA drugs, quinolones, carbapems, and aminoglycosides were used as combined antibiotics.

DISCUSSION

This retrospective study showed differences in baseline characteristics, disease severity, identified pathogens, initial antibiotic regimens, and clinical outcomes between patients with HCAP and those with CAP.

Among the 14 patients with HCAP, seven (50%) had been hospitalized for at least 2 days in the preceding 90 days and five (35.7%) resided in a nursing home or extended care facility. Shindo *et al.* reported that 39% of patients with HCAP had been hospitalized for at least 2 days in the preceding 90 days and 61.0% resided in a nursing home or extended care facility [12]. Maruyama *et al*. reported that in a rural region of Japan where the population over 65 years of age represents 30% of the population, 69.4% were patients with HCAP (NHAP) and 30.6% were patients with HAP [16]. Although the proportion of patients with NHAP in our studies was relatively low, it may be due to differences in the character of each hospital and local environment.

We found that patients with HCAP were older than those with CAP, results that support two studies from Japan [12, 16]. Complications were also more frequently found in patients with HCAP. Among these complications, central nerve diseases were more prevalent

in patients with HCAP, while chronic lung diseases and heart disease were more prevalent in patients with CAP. These characteristics were similar to the reports of Murayama *et al.* [16], but much different from the results in the United States [4-5] suggesting a high frequency of aspiration pneumonia in elderly patients with old brain infarction in Japan.

Physical examinations and laboratory findings of patients with HCAP were similar to those of patients with CAP, but patients with HCAP were older and had significantly lower serum albumin level compared to those with CAP. In addition, greater disease severity was found in patients with HCAP compared to those with CAP. We did not find significant different mortality between HCAP and CAP in this study (21.4% vs. 10.0%, respectively: p=0.3544, data not shown), however, lower serum albumin was related with mortality in patients with HCAP (P<0.0308, data not shown). Malnutrition may be one of the most important factors that affects prognosis apart from being a risk factor for pneumonia[17-18].

It strongly suggested that a lower serum albumin level is related with elderly age and lower performance status of patients with NHAP [16], and in other study of NHAP, poor functional status has been also correlated with the presence of MDR pathogens [18]. We did not investigate patients' performance status in this study; however, performance status may be a potential prognosis factor for patients with HCAP. Further investigation is needed.

We isolated more MRSA, Pseudomonas spp. and anaerobes in patients with HCAP; however, *S. pneumonia* was more frequently isolated and penicillin was more frequently administered in patients with CAP in this study. Furthermore, the larger number of anaerobes suggested a higher incidence of aspiration pneumonia in patients with HCAP in Japan and was related with older age, central nerve diseases rates, and hypoalbuminemia in these patients.

We previously reported that HAP in Japan included a large number of mild to moderate cases of aspiration pneumonia and these patients received excessive antibiotic therapy, although most cases of HAP in the United States were moderate to severe ventilator-associated pneumonia and physicians responded with strong antibiotic therapy, *e.g.* de-escalation therapy [11, 15]. In Japan, hospitals serve not only as acute care facilities, but also as nursing homes. Patients who have chronic diseases in Japan usually stay much longer in hospitals than those in the United States. This is one of the most important reasons for the high incidence of aspiration pneumonia in cases of HAP in Japan.

Moreover, these patients were usually delivered to emergency hospitals and counted and treated as having CAP. Previously, a substantial number of patients with HCAP were counted and treated as having CAP [3-4].

The results of this study justify the separation of a new type of pneumonia, HCAP, from the traditionally defined CAP domain. HCAP is distinct from CAP in terms of patient characteristics, pathogen distribution patterns, and clinical outcomes. HCAP is also different from HAP and ventilator–associated pneumonia along the above-mentioned dimensions; however, in general, HCAP differs from HAP and ventilator–associated pneumonia to a lesser degree than from CAP. Given that the data in this study were derived from a consortium of hospitals typical of acute care hospitals in Japan, it is reasonable to expect that at the present time, a large proportion of patients hospitalized in acute-care facilities are being treated for CAP but in fact should be treated for HCAP, resulting in potentially poor clinical outcomes.

Craven and Zilberberg *et al.* emphasized that the early initiation of appropriate and adequate antibiotic therapy was important for improving the outcomes of patients with HCAP [19-20]. In this study, the data suggest that patients with HCAP tended to have risk factors for MRSA, which should be treated with vancomycin or linezolid, as recommended by the 2005 ATS/IDSA-HAP guidelines [1], even if the patients are not classified as having a severe disease. Therefore, HCAP should be identified as a distinct entity in determining the initial empirical antibiotic treatment, as stated in recent reports [3].

In conclusion, we found that patients with HCAP were significantly older and had more central nerve diseases than those with CAP. MRSA and anaerobes were more frequently identified from patients with HCAP than from patients with CAP. These results provide additional evidence that HCAP should be distinguished from CAP. Moreover, we showed that the occurrence of malnutrition, including hypoalbuminemia might have the potential to be a prognosis factor. Diagnostic and therapeutic strategies for HCAP may be the key to improving mortality in patients with HCAP and physicians need to consider MRSA and anaerobic pathogens in choosing the initial empirical antibiotic treatment of HCAP.

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CONFLICTS OF INTERESTS

No conflicts of interests were declared in relation to this article.

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TABLES

Table 1. Subject demographics patients with healthcare-acquired pneumonia and those with community-acquired pneumonia

	CAP (n = 20)	HCAP (n = 14)	p-value	
Age (years)	53.8±19.5	77.2±9.7	0.0001***	3)
Sex (male/female)	12/8	8/6	0.8002	1)
Complications	15 (75.0%)	14 (100.0%)	0.0428*	1)
Chronic lung diseases	10/20 (50.0%)	7/14 (50.0%)	1.0000	2)
Chronic heart diseases	2/20 (10.0%)	1/14 (7.1%)	0.6350	2)
Neoplastic diseases	0/20 (0.0%)	2/14 (14.3%)	0.0815	1)
Central nerve diseases	0/20 (0.0%)	4/15 (28.6%)	0.0216*	2)
Liver diseases	2/20 (10.0%)	1/14 (7.1%)	0.6350	2)
Collagen diseases	1/20 (5.0%)	1/14 (7.1%)	0.6613	2)
Diabetes mellitus	4/20 (20.0%)	1/14 (7.1%)	0.2975	1)

Age is expressed as means± SD. [#]Includes overlapping cases. CAP, community-acquired pneumonia; HCAP, healthcare–associated pneumonia

[1)]χ2-test, [2)]Fisher's exact-test, [3)]t-test; *p<0.05, **p<0.01, ***p<0.001.

Table 2 Clinical data of patients with healthcare-acquired pneumonia and those with community-acquired pneumonia#

	CAP (n = 20)	HCAP (n = 14)	p-value	
Body Temperature, °C	37.0±1.0	37.7±1.4	0.7392	2)
Heart rate, /min	90.7±19.2	83.3±14.5	0.2317	2)
Respiratory rate, /min	22.1±5.8	26.9±8.4	0.0588	3)
Dehydration	16 (80.0%)	12 (85.7%)	0.6678	1)
Disorientation	6 (30%)	7 (50%)	0.2376	1)
WBC, /mm^3	11125.6±9514.3	10072.1±3687.3	0.5386	3)
Albumin, mg/dl	3.70±0.42	3.06± 0.64	0.0050**	3)
CRP, mg/dl	6.4±3.0	8.2±2.3	0.4785	3)
SpO_2, %	93. 5± 0.8	91.0±7.3	0.2452	3)
Chest Infiltrates[#]:			0.0452*	1)
>2/3	1 (5.0%)	3 (21.4%)		
Middle	2 (10.0%)	5 (35.7%)		
<1/3	17 (85.0%)	6 (42.6%)		
PSI	59.3±22.7	91.5±16.9	0.0001***	2)
A-DROP			0.2820	1)
Severe	2 (10.0%)	8 (57.1%)		
Moderate	12 (60.0%)	6 (42.9%)		
Mild	6 (30.0%)	0 (0.0%)		
I-ROAD			0.0162*	3)
Severe	9 (45.0%)	12 (85.7%)		
Moderate	0 (0.0%)	0 (0.0%)		
Mild	11 (55.0%)	2 (14.3%)		

Body temperature, blood pressure, respiratory rates, and white blood cell count (WBC) are expressed as means±SD. CAP, community-acquired pneumonia; HCAP, healthcare–associated pneumonia; C-reactive protein; SpO_2, saturation of peripheral oxygen. [#]Includes overlapping cases [1)]χ2-test, [2)]Wilcoxon's rank test, [3)]t-test; *p<0.05, **p<0.01.

Table 3 Microbes identified in patients with healthcare-acquired pneumonia and those with community-acquired pneumonia#

Microbes	CAP Patients (n = 20)	HCAP Patients (n = 14)	p-value
Gram-negative pathogens	5 (25.0)	4 (28.6)	0.5718 2)
Klebsiella species	0 (0)	1 (7.1)	0.2251 1)
ESBLs	0 (0)	0 (0)	
Pseudomonas species	0 (0)	3 (21.4)	0.0302* 1)
Escherichia coli	0 (0)	0 (0)	
Haemophilus influenzae	2 (10.0)	0 (0)	0.1291 1)
Moraxella catarhalis	3 (15.0)	0 (0)	0.0886 1)
Other Gram-negative bacteria	0 (0)	0 (0)	
Gram-positive pathogens	14 (70.0)	8 (57.1)	0.3404 2)
Streptococcus pneumoniae	13 (65.0)	3 (21.4)	0.0399* 2)
MSSA	1 (5.0)	0 (0)	0.3958 1)
MRSA	0 (0)	3 (21.4)	0.0302* 1)
Atypical pathogens	1 (5.0)	0 (0)	0.3958 1)
Chlamydophila pneumoniae	0 (0)	0 (0)	
Mycoplasma pneumoniae	0 (0)	0 (0)	
Legionella pneumophila	0 (0)	0 (0)	
Influenza virus	2 (10.0)	3 (21.4)	0.1621 1)
Anaerobes	0 (0)	3 (21.4)	0.0302* 1)

#Includes overlapping cases

CAP, community-acquired pneumonia; HCAP, healthcare–associated pneumonia; ESPLs, extended-spectrum β-lactamase producing bacteria; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*.

1)χ2-test; 2)Fisher's exact-test; *$p<0.05$.

Table 4. Antibiotic treatment of patients with healthcare-acquired pneumonia and those with community-acquired pneumonia [#]

Therapy and outcomes	CAP Patients (n = 20)	HCAP Patients (n = 14)	p-value	
Monotherapy	18 (90.0)	11 (78.5)	0.6613	2)
Penicillin	13 (65.0)	2 (14.2)	0.0145*	2)
3rd or 4th Cefems	3 (15.0)	3 (21.6)	0.2486	1)
Carbapenems	2 (10.0)	3 (21.6)	0.1621	1)
Quinolones	0 (0)	1 (7.1)	0.2251	1)
Anti-MRSA	0 (0)	2 (14.2)	0.1291	1)
Combination therapy	2 (10.0)	3 (21.6)	0.1621	1)
Carbapenems + Anti-MRSA	0 (0)	1 (7.1)	0.2251	1)
Carbapenems + Quinolones	0 (0)	1 (7.1)	0.2251	1)
Clindamycin + 3rd Cefems	1 (5.0)	0 (0)	0.3958	1)
Clindamycin + Quinolones	1 (5.0)	0 (0)	0.3958	2)
Aminoglycoside + Anti-MRSA	0 (0)	1 (7.1)	0.2251	1)

[#]Includes overlapping cases

CAP, community-acquired pneumonia; HCAP, healthcare–associated pneumonia; anti-MRSA, anti-methicillin-resistant *Staphylococcus aureus*.

[1)]χ2-test; [2)]Fisher's exact-test; *$p<0.05$