ORIGINAL

Difference of health-care associated pneumonia between large hospitals and small hospitals in Japan

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ABSTRACT : Objective : Health-care associated pneumonia (HCAP) is a new category of pneumonia. We investigated differences of epidemiology, pathogens, and outcomes between HCAP patients in large hospitals and those in small hospitals. Methods : This was a retrospective observational study of patients hospitalized with HCAP from December 2009 to March 2010. HCAP was defined according to ATS/IDSA criteria. A large hospital was defined as ≥200 beds and a small hospital was <200 beds. Results : Of 117 patients, 61 patients were admitted to large hospitals and 56 patients were admitted to small hospitals. There was a significant difference of HCAP diagnostic criteria between the two groups. The A-DROP severity class was worse in the large hospital group than the small hospital group ($P<0.05$). Respiratory failure and disturbance of consciousness were more frequent in the large hospital group ($P<0.05$). The mortality rate was 8.2% in the large hospital group versus 1.8% in the small hospital group. Patients in the very severe A-DROP class had a high mortality rate of 33% in both groups. Conclusion : Patients with severe HCAP were more likely to be admitted to large hospitals. Patients in the very severe A-DROP class should receive intensive antibiotic therapy, but not all patients need broad-spectrum therapy. J. Med. Invest. 58 : 67-74, February, 2011

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INTRODUCTION

Pneumonia is one of the most common diseases requiring hospitalization. It remains an important cause of morbidity and mortality despite various advances in diagnosis, antibacterial therapy, critical

care, and supportive care, especially in elderly patients and patients with required hospitalization (1). Pneumonia was previously classified into community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP). Recently, health-care associated pneumonia (HCAP) was defined as a form of HAP or nosocomial pneumonia by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) (2). In general, patients with HCAP are more similar to those with HAP and VAP than those with CAP, because they have a greater burden of comorbidities, including cancer, chronic kidney disease, heart disease, chronic obstructive pulmonary disease, dementia, and impaired mobility (3)-(5). The pathogens that cause HCAP are more likely to be resistant to multiple antibiotics, as is the case for HAP and VAP (3) (6). Therefore, it is considered that the initial treatment of HCAP should be similar to that of HAP or VAP rather than that of CAP. Carratala *et al*. reported that the most common causative organism for both CAP and HCAP was *Streptoccous pneumonia* (7), while *Staphylococcus aureus* and gram-negative bacilli (except for *Hemophilus species*) were less common than in other reports and no gram-negative bacilli producing extended-spectrum β-lactamases were found. The clinical features of HCAP vary among reports. In Japan, only limited data about HCAP have been published so far. In the present study, we investigated differences of epidemiology, causative organisms, antibiotic susceptibility, and outcome between patients with HCAP who were admitted to small hospitals versus large hospitals.

MATERIAL AND METHODS

Patients

A total of 117 patients hospitalized for HCAP were recruited from December 1, 2009 through April 31, 2010. The study was conducted at eight hospitals in Japan (Motomachi Hospital, Tottori University Hospital, Matsue Red Cross Hospital, Matsue General Hospital, San-in Rosai Hospital, Saihaku Hospital, Chukai Clinic, and Yoka Hospital). Tottori University Hospital, Matsue Red Cross Hospital, Matsue General Hospital, San-in Rosai Hospital, and Yoka Hospital each have more than 200 beds, while Motomachi Hospital, Saihaku Hospital, and Chukai Clinic each have less than 200 beds. In Japan, hospitals are classified by medical law into three groups : (1) general hospital which has less than 200 beds, (2) community supporting hospital which has more than 200 beds, and (3) advanced treatment hospital. In this study, a large hospital was defined as ≥200 beds and a small hospital was <200 beds. In the large hospitals, only patients who received treatment from chest physicians were enrolled (large hospital group). In contrast, all patients hospitalized for HCAP in the small hospitals were enrolled (small hospital group), and 13 patients received treatment from chest physicians.

Evaluation

Diagnosis of pneumonia required the presence of new radiographic infiltrates plus at least two of the following : (1) a white blood cell (WBC) count $>9{,}000\times10^3/\mu l$ or $<3{,}000\times10^3/\mu l$; (2) a body temperature ≥ 38°C, and (3) purulent secretions from the lower respiratory tract. Based on the ATS/IDSA guidelines (2), HCAP was defined as pneumonia in a patient with at least one of the following risk factors : (1) hospitalization in an acute care hospital for two or more days in the last 90 days ; (2) residence in a nursing home or long-term care facility in the last 90 days ; (3) receiving outpatient intravenous therapy (like antibiotics or chemotherapy) within the past 30 days ; (4) receiving home wound care within the past 30 days ; (5) attending a hospital clinic or dialysis center in the last 30 days ; and (6) having a family member with known multidrug resistant pathogens. The outcome measures evaluated were 30-day survival or discharge from the hospital within 30 days.

The clinical efficacy of therapy was determined from improvement of pneumonia based on at least three of the following : (1) improvement of chest X-ray findings compare with those at the start of therapy ; (2) a decrease of body temperature to 37°C ; (3) a decrease of the WBC count to $<9{,}000\times10^3/\mu l$ and a decrease of C-reactive protein (CRP) to <30% of the pretreatment value (8). The severity of pneumonia was graded according to the Japan Respiratory Society (JRS) 2005 classification of the severity of CAP (9), which assesses the age, dehydration, respiratory failure, disturbance of consciousness, and low blood pressure (A-DROP score).

Microbiology

Sputum from the respiratory tract was used for the identification of pathogens according to JRS guidelines (9). The diagnosis was confirmed by Gram-staining with phagocytosis and collected heavy

growth (3+ ; adapted from 1×10^5 cfu/ml to 1×10^7 cfu/ml of sample). Single or paired sera were used to detect antibodies against *Mycloplasma pneumoniae* and *Chlamydia pneumoniae*. *Legionella pneumophilia* serogroup I antigen was detected in urine samples by immunochromatography (NOW *Legionella* Urinary Antigen Test ; Binax Inc., United States).

Data analysis

Results are shown as the mean± standard error (SE). SPSS software (Japanese version 16.0 for Windows ; SPSS Japan Inc., Tokyo, Japan) was used for statistical analysis. Comparisons between groups were done with the Mann-Whitney nonparametric test, while the χ^2 test was employed for categorical data. Significance was defined as $p<0.05$ for all analyses.

RESULTS

Patient characteristics

During the study period, 117 adults with HCAP were hospitalized, with 61 patients being admitted to large hospitals (≥200 beds) and 56 patients being admitted to small hospitals (<200 beds). The characteristics of patients from the large hospital group and the small hospital group are compared in Table 1. The large hospital group had more male patients than the small hospital group. Among the HCAP criteria, outpatient intravenous therapy had been received by 21.3% in the large hospital group versus 5.4% in the small hospital group, while the frequency of attending a hospital clinic or dialysis center was 39.3% in the large hospital group versus 7.1% in the small hospital group, and there were significant differences between the two groups (*P< 0.05*). However, there was a significant difference in the prevalence of chronic heart disease (*P< 0.05*). In addition, respiratory failure and impaired consciousness were more frequent in the large hospital group compared with the small hospital group (*P< 0.05*). As a result, the large hospital group had more severe disease than the small hospital group (*P< 0.05*) according to the A-DROP classification. There was also a significant difference in the use of antibiotic therapy before hospitalization by two groups (*P< 0.05*).

Causative pathogens

The causative pathogens in the large hospital group and the small hospital group are shown in Table 2. The percentage of patients with a confirmed etiologic diagnosis was not significantly different

Table 1 Main Clinical Characteristics of Patients by Epidemiological Group

Characteristic	Large hospital group (≥200 beds)	Small hospital group (<200 beds)	*P value*
Number	61	56	
Age (year)	82.9 ±10.0	85.9 ± 9.5	NS
Gender (male/female)	41/20	26/30	*P<0.05*
Food intake			
Oral	50 (82.0%)	44 (78.6%)	NS
PEG	11 (18.0%)	12 (21.4%)	NS
Tube feeding	0 (0%)	0 (0%)	NS
Comorbid conditions [a]			
COPD	6 (9.8%)	4 (7.1%)	NS
Chronic heart disease	14 (23.0%)	6 (10.7%)	*P<0.05*
Diabetes mellitus	4 (6.6%)	1 (1.8%)	NS
Cerebrovascular disease	19 (31.1%)	21 (37.5%)	NS
Cancer	3 (4.9%)	1 (1.8%)	NS
Chronic renal failure	2 (3.3%)	0 (0%)	NS
Autoimmune disease	3 (4.9%)	0 (0%)	NS
Dementia	45 (73.8%)	52 (92.6%)	NS
HCAP criteria [a]			
Hospitalization for ≥ 2 d in the last 90 d	19 (31.1%)	14 (25.0%)	NS
Residence in a nursing home or long-term care facility	40 (65.6%)	48 (85.7%)	NS
Receiving outpatient intravenous therapy	13 (21.3%)	3 (5.4%)	*P<0.05*
Receiving home wound care	1 (1.6%)	0 (0%)	NS
Attending a hospital clinic or dialysis center	24 (39.3%)	4 (7.1%)	*P<0.05*
Having a family member with known MDR pathogens	0 (0%)	0 (0%)	NS
Prior antibiotic therapy before hospitalization	13 (21.3%)	7 (12.5%)	*P < 0.05*
Dehydration	27 (44.3%)	23 (41.1%)	NS
Respiratory failure (SpO_2<90%)	25 (41.0%)	11 (19.6%)	*P<0.05*
Disturbance of consciousness	39 (63.9%)	13 (23.2%)	*P<0.05*
Low blood pressure (Systolic BP ≤ 90mmHg)	2 (3.3%)	3 (5.4%)	NS
A-DROP severity class			*P<0.05*
Mild	4 (6.6%)	2 (3.6%)	
Moderate	28 (45.9%)	42 (75.0%)	
Severe	17 (27.9%)	9 (16.1%)	
Very severe	12 (19.7%)	3 (5.3%)	

Value are the mean ± SE. PEG: percutaneous endoscopic gastrostomy, [a] Including overlapping cases, NS: not significant, SpO_2: pulse oximetric saturation,

Table 2 Etiology in 117 Cases of Pneumonia by Epidemiological Group

Etiology	Large hospital group (≥ 200 beds) (n=61)	Small hospital group (< 200 beds) (n=56)
Gram-positive pathogen	7 (11.5%)	14 (25.0%)
Streptococcus pneumoniae	2 (3.3%)	4 (7.1%)
Staphylococcus aureus	3 (4.9%)	3 (5.4%)
MSSA	3 (4.9%)	2 (3.6%)
MRSA	0 (0%)	1 (1.8%)
Streputococci other	2 (3.3%)	4 (7.1%)
Gram-negative pathogen	12 (19.7%)	7 (12.5%)
Klebsiella species	3 (4.9%)	2 (3.6%)
Pseudomonas species	2 (3.3%)	0 (0%)
Escherichia coli	1 (1.6%)	3 (5.4%)
Moraxella catarrhalis	2 (3.3%)	1 (1.8%)
Heamophilus species	4 (6.6%)	0 (0%)
Enterobacter cloacae	0 (0%)	1 (1.8%)
Atypical pathogen		
Chlamydophila pneumoniae	0 (0%)	0 (0%)
Mycoplasma pneumoniae	0 (0%)	0 (0%)
Legionera pneumophilia	0 (0%)	0 (0%)
No pathogen identified	42 (68.6%)	38 (67.9%)

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-sesitive *Staphylococcus aureus*

between the two groups (31.4% in the large hospital group versus 32.1% in the small hospital group). Gram-positive pathogens were more frequently isolated in the small hospital group than in the large hospital group. In the small hospital group, gram-positive pathogens were more frequent than gram-negative pathogens. In contrast, there was no significant difference in the frequency of pathogens in the large hospital group. Atypical pathogens were not detected in either group.

Antibiotic therapy and clinical outcome

Table 3 shows the antibiotic therapy provided and the outcome. More than 94% of the patients received β-lactam monotherapy in both the small hospital group and the large hospital group. There were no differences of initial antibiotic therapy between the large and small hospital groups. The rate of initial treatment failure was 13.1% in the large hospital group versus 17.9% in the small hospital group, with no significant difference between the two groups. A similar percentage of patients in both groups had a relapse after apparently successful treatment. There was also no difference between the two groups with regard to the duration of therapy.

The overall death rate was 8.2% in the large hospital group and 1.8% in the small hospital group. In the large hospital group, one patient died within 48 hours of hospitalization due to respiratory failure. The early and overall death rates were not significantly different between the two groups. Table 4 shows the details of the fatal cases. Five out of 6 patients who died were in the very severe A-DROP class and one patient was severe. Overall, 12 patients belonged to the very severe class in the large hospital group versus 3 patients in the small hospital group (Table 1). The mortality rate of patients from the very severe A-DROP class was 33.3% in both groups (4/12 patients in the large hospital group versus 1/3 patients in the small hospital group). In contrast, no patient died in either group when the A-DROP class was moderate or mild. All of the patients who died had comorbidities, including chronic heart failure in 2 patients, cerebrovascular disease in 2 patients, COPD in 1 patient, and autoimmune disease in 1 patient. In addition, all of them received β-lactam monotherapy. In 5 out of 6 patients, a causative pathogen was not identified.

Table 3 Antibiotic Therapy and Outcomes of Pneumonia by Epidemiological Group

Therapy and Outcomes	Large hospital group (≥ 200 beds) (n=61)	Small hospital group (< 200 beds) (n=56)	*P* value
Initial antibiotic therapy			NS
Monotherapy			
β-Lactams (number)	58 (95.1%)	53 (94.6%)	
Quinolones (number)	3 (4.9%)	0 (0%)	
Clindamycin (number)	0 (0%)	1 (1.8%)	
Combination therapy			
β-Lactams + quinolones (number)	0 (0%)	1 (1.8%)	
β-Lactams + glycopeptide (number)	0 (0%)	1 (1.8%)	
Initial treatment failure (number)	8 (13.1%)	10 (17.9%)	NS
Length of therapy (day)	8.0 ± 3.9	8.5 ± 2.2	NS
Relapse case (number)	4 (6.6%)	1 (1.8%)	NS
Early case –fatality rate, < 48 h (number)	1 (1.6%)	0 (0%)	NS
Overall case-fatality rate, < 30d (number)	5 (8.2%)	1 (1.8%)	NS

Value are the mean ± SE: NS = not significant.

Table 4 Characteristics in Fatality Cases

Age/ Gender	Initial antibiotic therapy	Duration to fatality	A-DROP severity class	Hospital group	Etiology	Comorbid conditions
95/female	β-Lactams	2 days	Very severe	Large	Not identified	Autoimmune disease
97/female	β-Lactams	< 1 week	Severe	Large	Not identified	Chronic heart disease
84/male	β-Lactams	< 1 week	Very severe	Large	*Escherichia coli*	COPD
95/female	β-Lactams	< 1 week	Very severe	Large	Not identified	Cerebrovascular disease
81/female	β-Lactams	< 2 weeks	Very severe	Large	Not identified	Cerebrovascular disease
95/male	β-Lactams	< 3 weeks	Very severe	Small	Not identified	Chronic heart disease

Abbreviations: COPD = Chronic obstructive pulmonary disease; Large, a hospital which had ≥ 200 beds; Small, a hospital which had < 200 beds.

DISCUSSION

This study showed that > 90% of the patients hospitalized with HCAP survived and that the A-DROP severity class closely reflected the risk of mortality in both the small hospital group (< 200 beds) and the large hospital group (≥200 beds). Approximately 33% of the patients in the very severe A-DROP class died within 30 days of hospital admission in both groups and > 10% of patients failed to respond to initial antibiotic therapy in both groups. Compared with the small hospital group, the large hospital group had a higher percentage of patients with respiratory failure and disturbance of consciousness, more male patients, and more high-risk patients. There was also a significant difference in the frequency of antibiotic therapy before hospitalization and the HCAP criteria between the two groups.

In recent years, the increase of patients who are elderly and severely disabled has led to the introduction of a new category of pneumonia known as health-care associated pneumonia (HCAP) (10). However, there is limited information to validate HCAP and a substantial number of HCAP patients

can be defined as having community-associated pneumonia (CAP) (2, 6). Various changes to the health system have shifted a considerable part of patient care from the hospitals to the community. In addition, there are marked differences of medical management and the health care system between countries. As a result, the epidemiology and outcome of HCAP have not necessarily shown agreement in various studies (6, 11-14). In this study, we evaluated differences in the epidemiology and outcome of HCAP between large and small hospitals in Japan.

In this study, we found that the large hospital group had more patients with severe and very severe pneumonia than the small hospital group. There are two possible reasons for this result. One is that the type of hospital was selected by the family or the staff of the residential facility based on the condition of the patient, and the other is the higher percentage of patients receiving antibiotics before hospitalization in the large hospital group. Patients were also more likely to have respiratory failure or disturbance of consciousness in the large hospital group compared with the small hospital group, suggesting that family members or staff took the patients to larger hospitals when their condition was more severe since large hospitals have better facilities and emergency units. In contrast, the family or staff would be more likely to take the patients to smaller hospitals when their condition was mild. It should be noted that hospitals can be selected freely by the patient or family under the Japanese national health system. Some patients received antibiotic therapy at home or in their residential care facility and they might be preferentially taken to large hospitals rather than small hospitals when the initial antibiotic treatment failed. The reported mortality rate of HCAP varies among studies (6, 11-14), suggesting that there are considerable differences in the severity of patients with HCAP presenting to different institutions.

In this study, we did not find a difference of mortality between the large hospital group and the small hospital group, possibly because the number of patients in this investigation was small. We did find that patients with severe HCAP tended to be admitted to large hospitals more often than small hospitals and that patients with very severe pneumonia had a high mortality rate in both groups. Therefore, a significant difference of the mortality rate may have been detected between the large hospital group and the small hospital group if the number of patients was increased.

A severity classification for HCAP has not been established yet. In this study, the A-DROP severity class corresponded to the mortality rate in both the small hospital group and the large hospital group. Among 6 patients who died, five were classified as very severe and one patient was in the severe class. However, it is likely that there would be lower correspondence with a pneumonia risk classification like CURB-65 or the pneumonia severity index (14-17). This is because the risk factor of drug-resistant pathogens (DRPs) is not reflected in the pneumonia severity classification. We considered that a possible reason for the correspondence of the A-DROP severity class with mortality was the low rate of DRPs in this series. On the other hand, El Solh *et al*. reported the effectiveness of a classification tree with ADL for predicting the risk of DRPs in patients with nursing home-acquired pneumonia (16). It may be necessary to establish a severity classification for HCAP based on ADL instead of age, because our patients with HCAP were much older than patients with CAP.

In this series, the 6 patients who died were all in the very severe (n=5) or severe (n=1) A-DROP class and all of them received β-lactam monotherapy. In contrast, most of the patients in our series responded to β-lactam monotherapy. Brito *et al*. reported that HCAP was a heterogeneous disease, so all patients did not need the same broad-spectrum antibiotic therapy as that given for complex nosocomial pneumonia (14). It has been emphasized in the literature that early initiation of appropriate and adequate antibiotic therapy is important for improving the outcome of patients with HCAP (18-20). Although recommended therapy for HCAP based on an existing pneumonia severity classification has not been established, it seems important to treat patients with a β-lactam plus a macrolide or quinolone or with three antibiotics if their A-DROP class is severe or very severe irrespective of the size of the hospital to which they are admitted.

In this study, the mortality rate was 8.2% in the large hospital group versus only 1.8% in the small hospital group. The mortality rate in both groups was low compared with the rates in other studies of HCAP (11-12). Labelle *et al*. reported that patients with culture-negative HCAP had less severe illness, a lower hospital mortality, and a shorter length of hospital stay compared with culture-positive patients (21). Venditti *et al*. reported that establishing a microbiological diagnosis of pneumonia was associated

with a higher in-hospital death rate by univariate analysis, but not multivariate analysis, in patients with CAP and HCAP. Some studies of CAP have suggested that establishing an etiologic diagnosis may not significantly influence the outcome, including the length of hospital stay or mortality (22, 23). The frequency of identified causative pathogens in this study was 31.6%, which was lower than in the other studies (6-7, 11-12), so the low mortality in this study may be associated with the fact that a causative organism was not identified in 68.4% of the patients. Thus, the frequency of aspiration pneumonia might have been high in both groups in the present study.

Other studies documented that potentially drug-resistant (PDR) pathogens occurred frequently among HCAP (1, 3, 6). However, in this study, the frequency of identified PDR pathogens was 4 out of 117 patients, and lower than other studies. Pathogens in 5/6 patients of fatality cases were not identified. It might be that PDR pathogens were causative organism in five fatality cases. Our study had certain limitations that should be acknowledged, because a number of patients were relatively small. Therefore, our result should be interpreted with caution.

In conclusion, our findings suggested that the characteristics of patients with HCAP are different between those admitted to large hospitals or small hospitals, especially with regard to the severity of pneumonia. Patients in the very severe A-DROP class have a much higher mortality rate compared with those in other classes and such patients require intensive antibiotic therapy. On the other hand, not all patients with HCAP need the broad-spectrum antibiotics. Further studies of a larger number of patients from hospitals of different sizes are needed confirm our findings.

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