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Etiology and Factors Contributing to Mortality in Healthcare-associated Pneumonia : A Single-center Study

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Abstract : Factors contributing to mortality in healthcare-associated pneumonia (HCAP) have not been investigated fully. We reviewed the etiology and identified prognostic factors of HCAP in hospitalized patients. We conducted a retrospective study of 500 Japanese patients with HCAP to assess these factors, with special emphasis on microbial etiology. Patients with HCAP were older (73.4 ± 11.4 years), more predominantly male (74.4%), and had more smoking history and comorbidity than did community-acquired pneumonia (CAP) patients. Microbes were identified in 52.8% of HCAP patients. The most frequent causative microbial agents were *Streptococcus pneumoniae* (n = 108, 21.6%), influenza virus (n = 47, 9.4%), and *Pseudomonas aeruginosa* (n = 40, 8.0%). Multiple drug-resistant (MDR) pathogens were more frequent in HCAP patients (9.8%) than CAP patients. Overall, 47 HCAP patients (9.4%) died, with mortality being higher in HCAP than CAP patients. The three leading causes of non-survival from HCAP were *S. pneumoniae*, influenza virus, and *P. aeruginosa*. MDR pathogens accounted for 21.3% of non-survivors. Multivariate analysis revealed disease severity on admission and treatment failure of initial antibiotics as independent factors for 30-day mortality. Among patients with treatment failure of initial antibiotics, 29.9% had received appropriate antibiotics. The most frequent pathogens in HCAP were *S. pneumoniae*, influenza virus, and *P. aeruginosa*, in both survivors and non-survivors. Disease severity on admission and treatment failure of initial antibiotics were independent factors for mortality. MDR pathogens are important therapeutic targets to mitigate negative results, and treatment strategies other than antibiotic selection are also required.

Key words : healthcare-associated pneumonia, etiology, mortality, prognostic factors, influenza virus infection

Introduction

The 2005 guidelines of the American Thoracic Society / Infectious Diseases Society of America (ATS / IDSA) established the concept of healthcare-associated pneumonia (HCAP), describing a patient population with frequent healthcare contacts and therefore at high risk of contracting resistant organisms[1]. Data supporting the HCAP concept were derived from a retrospective

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Table 1. Number of patients in each ATS / IDSA 2005 HCAP category[1)]

Category	n	%
Hospitalization for 2 days or more in the preceding 90 days	95	19.0
Resided in a nursing home or long-term care facility	34	6.8
Received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection	99	19.8
Attended a hospital or hemodialysis clinic	429	85.8

ATS, American Thoracic Society; HCAP, healthcare-associated pneumonia; IDSA, Infectious Diseases Society of America.
Numbers and percentages add up to > 500 and > 100% because some patients have more than 1 risk factor.

2-year (2002–2003) cohort analysis of 4543 patients with pneumonia hospitalized in the United States[2)], and many patients had multiple drug-resistant (MDR) pathogen infections. However, in recent studies evaluating the etiology in patients with HCAP, the incidence of MDR pathogens was far lower than that reported in the previous study[2)].

HCAP patients are older and have a higher frequency of comorbidity[2–4)] than patients with community-acquired pneumonia (CAP), and chronic conditions in older adults are known to increase the risk of influenza complications. Thus, we assumed that influenza virus infection is not uncommon in HCAP; however, few studies have investigated the frequency of influenza virus infection in this condition. Thus, the aims of this study were to review the microbial etiology and frequency of influenza virus infection in HCAP and to identify factors contributing to mortality in patients with this disease.

Materials and methods

We performed a retrospective study of all patients hospitalized with HCAP at our institution in Saitama, Japan, from January 2002 to December 2011. Characteristics of HCAP patients were compared with those of CAP patients hospitalized in our institution during the same period[5)]. The study protocol was approved by the Ethics Committee of the Saitama Cardiovascular and Respiratory Center (2011027). Pneumonia was diagnosed on the basis of symptoms suggestive of lower respiratory tract infection and the development of infiltration on chest X-ray. HCAP was defined when the criteria of the ATS / IDSA guidelines[1)] were satisfied (Table 1), and severe HCAP was defined when at least one major criterion or three minor criteria of the IDSA / ATS guidelines[6)] were present. Patients with acquired immunodeficiency syndrome, tuberculosis, non-resected lung cancer, or a confirmed alternative diagnosis at the end of follow-up were excluded from the study.

Diagnosis of causative microorganisms was based on the results of semiquantitative cultures of respiratory samples or blood, paired sera, urinary antigen tests for *Streptococcus pneumoniae* and *Legionella pneumophila*, and nasopharyngeal swabs for influenza virus as reported previously[5)]. In this study, MDR pathogens included methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and

extended-spectrum β-lactamase-producing Enterobacteriaceae, based on previous reports showing problematic clinical outcomes for infections caused by these pathogens[1, 7].

Treatment prescribed during the first 24 h of hospitalization was considered the initial treatment. Concordant CAP therapy was defined according to established IDSA / ATS guidelines[6]. The treatment effect of initial antibiotics after admission was judged after the first 48～72 h of therapy, based on body temperature, arterial oxygen saturation measured with pulse oximeter (SpO_2) or arterial partial pressure of oxygen, and white blood cell count[8]. In cases of treatment failure, the appropriateness of administered antibiotics was judged by the *in vitro* susceptibility of cultured bacteria and coverage of atypical pathogens and influenza virus.

Variables assessed as possible risk factors for 30-day mortality of HCAP included : patient demographic factors, the presence of the comorbid diseases listed in Table 2, the presence of prior antibiotics administered by a local physician, causative pathogens, disease severity on admission, and initial treatment antibiotics.

Statistical analysis

Results are presented as the number and percentage or mean±standard deviation unless otherwise indicated. Risk factors for mortality from HCAP were evaluated by univariate and multivariate logistic regression analysis. Variables showing significance by univariate analysis were included in the multivariate logistic regression analysis with backward elimination method. The 95% confidence interval (CI) for all comparisons is also reported. In all instances, a 2-tailed P value of < 0.05 was considered to indicate statistical significance. All statistical analyses were performed with Statistical Analysis System software (SAS version 9.1.3 ; SAS Institute, Inc., Cary, NC).

Results

Overall, 500 patients were enrolled during the study period. Characteristics of the patients diagnosed as having HCAP are shown in Table 2. Patients with HCAP were older, more predominantly male, had more smoking history, more comorbidity, and had more frequently received long-term oxygen therapy and antibiotics prior to admission to our hospital than did patients with CAP.

Microbiological patterns

Diagnostic methods used and results obtained (positive cases / number tested) are listed in Table 3. The etiologic microorganisms of HCAP are shown in Table 4. Of the 264 patients (52.8%) with a pathogen identified, 40 had two or three pathogens. *S. pneumoniae* was the most frequent microorganism found in polymicrobial infections, with *S. pneumoniae* and influenza virus being the most frequent combination (Table 4). Of the 47 patients with influenza virus infection, 30 (63.8%) were diagnosed by positive rapid infuluenza diagnostic test (RIDTs), 10 (21.3%) were diagnosed by serology, and 7 (14.9%) were positive for both RIDT and serology. Eighteen of the 47 patients (38.3%) with influenza virus infection had polymicrobial infections

Table 2. Characteristics of patients with HCAP and CAP

Factor	CAP	HCAP	*P*-value
Patients	1032	500	−
Sex (male)	683 (66.2%)	372 (74.4%)	0.001
Age*	64.0 ± 18.3	73.4 ± 11.4	<0.001
Smoking habit	604 (58.5%)	342 (68.4%)	<0.001
Prior antibiotics, no	628 (60.9%)	348 (69.6%)	<0.001
Long-term oxygen therapy	23 (2.2%)	131 (26.2%)	<0.001
Comorbidity			
No	295 (28.6%)	35 (7.0%)	<0.001
Respiratory disease alone	268 (26.0%)	183 (36.6%)	
Systemic disease alone	274 (26.6%)	119 (23.8%)	
Both	195 (18.9%)	163 (32.6%)	
Respiratory diseases			
Chronic obstructive pulmonary disease	166 (16.1%)	164 (32.8%)	<0.001
Asthma	102 (9.9%)	48 (9.6%)	0.93
Bronchiectasis	55 (5.3%)	40 (8.0%)	0.05
Nontuberculous mycobacteria	36 (3.5%)	31 (6.2%)	0.02
Old pulmonary tuberculosis	54 (5.2%)	52 (10.4%)	<0.001
Chronic pulmonary aspergillosis	15 (1.5%)	10 (2.0%)	0.52
Interstitial pneumonia	43 (4.2%)	56 (11.2%)	<0.001
Post lung cancer operation	35 (3.4%)	23 (4.6%)	0.26
Pneumoconiosis	7 (0.7%)	7 (1.4%)	0.25
Pulmonary thromboembolism	4 (0.4%)	2 (0.4%)	1.00
Chronic empyema	4 (0.4%)	5 (1.0%)	0.16
Others	17 (1.6%)	13 (2.6%)	0.24
Systemic diseases			
Hypertension	114 (11.0%)	45 (9.0%)	0.25
Congestive heart failure	35 (3.4%)	40 (8.0%)	<0.001
Ischemic heart disease	33 (3.2%)	38 (7.6%)	<0.001
Diabetes mellitus	107 (10.4%)	63 (12.6%)	0.19
Valvular heart disease	10 (1.0%)	16 (3.2%)	0.003
Arrhythmia	42 (4.1%)	37 (7.4%)	0.009
Cerebrovascular disease	41 (4.0%)	39 (7.8%)	0.002
Dementia	13 (1.3%)	11 (2.2%)	0.19
Neuromuscular disease	10 (1.0%)	12 (2.4%)	0.04
Post upper digestive system surgery	29 (2.8%)	18 (3.6%)	0.43
Chronic liver disease	25 (2.4%)	12 (2.4%)	1.00
Connective tissue disease	41 (4.0%)	15 (3.0%)	0.39
Mental disorder	10 (1.0%)	4 (0.8%)	1.00
Malignancy	19 (1.8%)	9 (1.8%)	1.00
Steroid or immunosuppressant	61 (5.9%)	57 (11.4%)	<0.001
Alcoholism	5 (0.5%)	4 (0.8%)	0.49
Others	75 (7.3%)	36 (7.2%)	1.00
Severity, severe	133 (12.9%)	93 (18.6%)	0.004
Treatment effect of initial antibiotics			
2 or more antibiotics	651 (63.1%)	296 (59.2%)	0.15
Antipseudomonal drug, yes	293 (28.4%)	193 (38.6%)	<0.001
Guideline adherence, discordant	348 (33.7%)	196 (39.2%)	0.04
Failure	130 (12.6%)	97 (19.4%)	<0.001
Mortality	32 (3.1%)	47 (9.4%)	<0.001

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia.
Values are n (%), unless otherwise indicated; *mean ± standard deviation.

Table 3. Diagnostic methods and results

Method	No. of episodes studied	No. of positive diagnostic studies (%)
Paired sera	286	33 (11.5)
Rapid influenza diagnostic test	481	37 (7.7)
Urinary antigen (*Legionella pneumophila*, *Streptococcus pneumoniae*)	431	100 (23.2)
Culture		
Sputum	435	103 (23.7)
Transbronchial aspirate	13	3 (21.4)
Protected specimen brush	1	1 (100.0)
Bronchial washing	1	1 (100.0)
Bronchoalveolar lavage fluid	11	2 (18.2)
Blood	299	6 (2.0)
Pleural fluid	3	2 (66.7)

Table 4. Etiology of healthcare-associated pneumonia

	CAP		HCAP						
	Total (n=1032)		Total (n=500)			Severe (n=93)		Non-survivors (n=47)	
Etiology	n	(%)	n	(%)	*P*-value	n	(%)	n	(%)
Streptococcus pneumoniae	244	(23.6)	108	(21.6)	0.40	20	(21.5)	8	(17.0)
Influenza virus	96	(9.3)	47	(9.4)	1.00	13	(14.0)	6	(12.8)
Pseudomonas aeruginosa	32	(3.1)	40	(8.0)	<0.001	9	(9.7)	8	(17.0)
Haemophilus influenzae	45	(4.4)	23	(4.6)	0.90	4	(4.3)	0	(0.0)
GNEB	28	(2.7)	23	(4.6)	0.07	5	(5.4)	2	(4.3)
ESBL-producing	28	(2.7)	3	(0.6)	–	1	(1.1)	0	(0.0)
ESBL-nonproducing	0	(0.0)	20	(4.0)	–	4	(4.3)	2	(4.3)
Moraxella catarrhalis	10	(1.0)	8	(1.6)	0.32	2	(2.2)	1	(2.1)
Stenotrophomonas maltophilia	0	(0.0)	2	(0.4)	0.11	1	(1.1)	0	(0.0)
Acinetobacter sp.	1	(0.1)	1	(0.2)	0.55	0	(0.0)	0	(0.0)
MRSA	8	(0.8)	4	(0.8)	1.00	4	(4.3)	3	(6.4)
MSSA	3	(0.3)	4	(0.8)	0.23	1	(1.1)	0	(0.0)
Streptococcus sp.*	9	(0.9)	3	(0.6)	0.76	2	(2.2)	1	(2.1)
Atypical pathogen	191	(18.5)	45	(9.0)	<0.001	9	(9.7)	4	(8.5)
Legionella spp.	53	(5.1)	18	(3.6)	0.20	6	(6.5)	3	(6.4)
Mycoplasma pneumoniae	105	(10.2)	16	(3.2)	<0.001	2	(2.2)	1	(2.1)
Chlamydia psittaci	15	(1.5)	1	(0.2)	0.03	0	(0.0)	0	(0.0)
Chlamydia pneumoniae	22	(2.1)	10	(2.0)	1.00	1	(1.1)	0	(0.0)
Others	13	(1.3)	1	(0.2)	0.045	0	(0.0)	0	(0.0)

CAP, community-acquired pneumonia; ESBL, extended spectrum β-lactamase; GNEB, Gram-negative enteric bacilli; HCAP, healthcare-associated pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

* Indicates other than *Streptococcus pneumoniae*.

Table 5. Pathogens causing polymicrobial infections

Pathogens	Total (n)	Severe (n)	Non-survivors (n)
2 pathogens			
Streptococcus pneumoniae + influenza virus	7	0	1
S. pneumoniae + *Haemophilus influenzae*	5	2	0
S. pneumoniae + *Chlamydophila pneumoniae*	1	0	0
S. pneumoniae + *Legionella* spp.	1	0	0
S. pneumoniae + *Moraxella catarrhalis*	2	1	1
S. pneumoniae + MRSA	1	1	1
S. pneumoniae + GNEB	1	0	0
Influenza virus + *Mycoplasma pneumoniae*	1	1	1
Influenza virus + MRSA	1	0	0
Influenza virus + *H. Influenzae*	2	0	0
Influenza virus + *M. catarrhalis*	1	0	0
Influenza virus + GNEB	3	2	0
M. pneumoniae + *Pseudomonas aeruginosa*	1	0	0
P. aeruginosa + GNEB	3	0	0
P. aeruginosa + *Legionella* spp.	2	1	1
P. aeruginosa + MRSA	1	1	1
M. catarrhalis + *H. influenzae*	1	0	0
MRSA + *S. maltophilia*	1	1	0
3 pathogens			
S. pneumoniae + influenza virus + *Legionella* spp.	1	0	0
S. pneumoniae + *C. pneumoniae* + *M. catarrhalis*	1	1	0
S. pneumonia + influenza virus + *M. pneumoniae*	1	0	0
P. aeruginosa + GNEB + *C. pneumoniae*	1	0	0
P. aeruginosa + influenza virus + *Acinetobacter calcoaceticus*	1	0	0

GNEB, Gram-negative enteric bacilli; MRSA, methicillin-resistant *Staphylococcus aureus*.

(Table 5). Among these 47 patients, only 8 had received influenza vaccination.

There were no differences in the rates of etiology of single pathogens, polymicrobial infections, and unknown pathogens between CAP and HCAP patients ($P = 0.29$). MDR pathogens and atypical pathogens were found in 9.8% and 9.0% of patients, respectively. The frequency of MDR pathogens differed between HCAP and CAP (HCAP, 9.0% versus CAP, 3.4%), and atypical pathogens were more frequent in CAP than HCAP.

Etiology of severe HCAP

In the 93 patients with severe HCAP, the three most frequently isolated pathogens were *S. pneumoniae*, influenza virus, and *P. aeruginosa*. MDR pathogens and atypical pathogens were found in 15.1% and 9.7% of patients, respectively, and polymicrobial infections occurred in 15.1% of patients. In 10 of 13 patients with influenza virus infection, the virus was detected by RIDTs; paired sera could only be obtained in 6 patients and increased antibody titers were found in 4 patients.

Initial antibiotic treatment after admission

Of the 500 patients with HCAP, 296 (59.2%) received two or three antibiotics. An antipseudomonal drug was administered as initial antibiotic therapy in 38.6% of patients, and none received an anti-MRSA agent. Thus, according to the ATS / IDSA guidelines for HCAP, therapy was discordant in all patients[1]. In contrast, therapy concordant with CAP guidelines was administered to 304 of the HCAP patients (61.0%) (β-lactams plus macrolides, n = 258; plus tetracyclines, n = 10; fluoroquinolones with / without β-lactams and macrolides, n = 36), while it was not administered to 196 patients (β-lactams only, n = 184; macrolides only, n = 6; tetracyclines only, n = 2; β-lactams plus clindamycin, n = 4).

Neuraminidase inhibitors for influenza virus infection

Neuraminidase inhibitors (NIs) were administered to 33 of 47 patients (70.2%) with influenza virus infection, based on positive RIDT results in 30 patients and clinical findings with a negative RIDT result in 3 patients. Fourteen of the 30 patients received NIs within 48 h after onset based on RIDT results, whereas 3 patients received NIs within 48 h after onset based on clinical findings.

Outcomes

Treatment with initial antibiotics failed in 97 patients (19.4%). Of these 97 patients, 29 (29.9%) received appropriate antibiotics. Overall, 47 HCAP patients (9.4%) died. Among the 49 patients with MDR pathogen infections, treatment failure with initial antibiotics occurred in 18 patients (*P. aeruginosa*, n = 14; MRSA, n = 1; extended-spectrum β-lactamase-producing Gram-negative enteric bacilli, n = 1; MRSA + *S. maltophilia*, n = 1; MRSA + *P. aeruginosa*, n = 1). Among these 18 patients, 10 patients died, of whom 5 had received appropriate antibiotics. Mortality from HCAP was higher than that from CAP. The most frequently isolated pathogens in non-survivors were *S. pneumoniae*, *P. aeruginosa*, and influenza virus. MDR pathogens and atypical pathogens were found in 23.4% and 8.5% of non-survivors, respectively, and polymicrobial infection occurred in 12.8% of non-survivors. All 6 cases of influenza virus infection in non-survivors were detected by RIDT, but paired sera could only be obtained in 2 cases. Among the 6 non-survivors with influenza virus infection, 5 had not received influenza vaccination, 2 had not received NIs, and the remainder had received NIs 48 h or more after onset (Table 6).

Risk factors for mortality

Multivariate analysis revealed disease severity and failure of initial antibiotic therapy as independent risk factors for mortality (Table 7). CAP therapy was not associated with improved mortality by univariate analysis. Congestive heart failure, MRSA infection, and MDR pathogen infection were significant factors by univariate analysis but were nonsignificant factors by multivariate analysis. Infection with *S. pneumoniae* (odds ratio, 0.725; 95% CI, 0.283-1.639; $P = 0.55$), *P. aeruginosa* (odds ratio, 2.691; 95% CI, 1.001-6.508; $P = 0.05$), and influenza virus (odds ratio, 1.469; 95% CI, 0.481-3.774; $P = 0.54$) were not significant factors by univariate analysis.

Table 6. Characteristics of patients with influenza virus infection (n = 47)

	n	(%)
Age (y)*	73.3 ± 9.9	
Sex (male)	36	(76.6)
Smoking habit	32	(68.1)
Vaccination status		
Yes	8	(17.0)
Unknown	13	(27.7)
Polymicrobial infection	18	(38.3)
Comorbidity		
No	8	(17.0)
Respiratory disease alone	15	(31.9)
Systemic disease alone	10	(21.3)
Both	14	(29.8)
Severity, severe	13	(27.7)
Neuraminidase inhibitor administration	33	(70.2)
Within 48 h	17	(36.2)
Non-survivors	6	(12.8)

* Mean ± standard deviation

Table 7. Univariate and multivariate analysis of the risk of 30-day mortality in the study patients

			Univariate analysis			Multivariate analysis (final model)		
Factor	n	Non-survivors	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Congestive heart failure	40	9	3.213	(1.252, 7.576)	0.02			
Staphylococcus aureus (MRSA)	4	3	30.325	(2.379, 1621.079)	0.006			
MDR pathogen	45	10	3.217	(1.314, 7.321)	0.01			
Severity, severe	93	27	7.866	(3.995, 15.742)	<0.001	4.714	(2.230, 9.965)	<0.001
Treatment effect, failure	97	39	32.797	(14.230, 85.401)	<0.001	25.734	(11.235, 58.943)	<0.001

CI, confidence interval; MDR, multiple drug-resistant; MRSA, methicillin-resistant S. aureus; OR, odds ratio.
Values represent *P*-value for category against the reference. Values in brackets represent the value for the explanatory variable.

Discussion

We found that patients with HCAP and CAP differed in demographics, disease etiology and severity, and mortality. In the patients with HCAP, the most frequent microbial agents were *S. pneumoniae*, *P. aeruginosa*, and influenza virus. Severity on admission and treatment failure of initial antibiotics were independent risk factors for mortality.

S. aureus is reported to be the most frequent pathogen (46.7%) of HCAP, followed by *P. aeruginosa* (25.3%), *Klebsiella pneumoniae* (7.6%), and others[2]. However, only culture-positive cases were analyzed. In the present study, urinary antigen tests, serological analysis, and RIDT

were also used in the etiological diagnosis, with cases of unknown etiology also included. More recent studies have revealed that the most frequent pathogen is *S. pneumoniae*, and atypical pathogens have been detected in 0.7% to 16.1% of cases[3, 4, 9–12]. In the present study, *S. pneumoniae* was the most frequent pathogen of HCAP, and the frequency of atypical pathogens was 9.0%, results compatible with those of previous reports[3, 4, 9–12]. Although the frequency of atypical pathogens was lower in HCAP than in CAP, the 9.0% incidence of atypical pathogens should not be ignored. The third leading pathogen was *P. aeruginosa*, indicating it to be certainly a major pathogen of HCAP.

We adopted RIDT and serological analysis to detect influenza virus infection as reported previously[5]. Previous studies have relied on the measurement of antibodies in paired serum samples, detection of viral antigen in both lower and upper respiratory tract samples[7, 13–17], and viral culture for diagnosis of viral pneumonia. Therefore, we included influenza virus in the etiology of HCAP according to these reports. However, it is important to mention the methodology of relying on testing of nasopharyngeal specimens for diagnosis of viral pneumonia because a virus detected in the nasopharynx may simply represent the presence of an upper respiratory infection or pneumonia antigen.

To our knowledge, there are only 4 reports[4, 10, 18, 19] which investigated influenza virus in HCAP. Carratalà *et al*[4] reported that influenza virus was detected in only 1 of 126 HCAP patients by serology, and Giannella *et al*[10] found influenza virus infection in 1 of 65 HCAP patients by RIDT and serology. However, a prospective study of Japanese nursing home residents reported detection of influenza virus in 14.7% of 75 cases by serology[11], and influenza virus accounted for 9.0% of our cases. These results suggest that influenza virus infection is not uncommon in HCAP, which may also be important information for infection control.

To our knowledge, only one report has described the etiology of severe HCAP[19]. That report introduced the polymerase chain reaction (PCR) method for etiological diagnosis and showed that *S. pneumoniae* and *S. aureus* (including MRSA) were the most frequent pathogens, followed by Gram-negative enteric bacilli and *P. aeruginosa*. Influenza virus infection accounted for 4.5% of pathogens, slightly lower than our results but suggesting that influenza virus infection is also not uncommon in severe HCAP. RIDT detected most of the cases of influenza virus infection in the patients with severe HCAP, whereas paired sera could only be obtained in 6 of 13 patients, indicating that when the diagnosis of influenza virus infection is based only on paired sera, cases with an acute clinical course or early death can be missed.

In the present study, disease severity was found to be an independent risk factor for mortality from HCAP. The three most widely studied criteria for severe pneumonia are the 20-variable Pneumonia Severity Index[20], the 5-variable CURB-65 score (the score is an acronym for each of the risk factors: Confusion, Urea $>$ 7 mmol / L, Respiratory rate $\geq$ 30 / min, low blood pressure, and Age $\geq$ 65)[21], and the 8-variable IDSA / ATS criteria[6]. We analyzed this study in accordance with the 8-variable IDSA / ATS criteria[6], which is reported to have similar prognostic power to the Pneumonia Severity Index[20] in HCAP patients[22], and disease severity on admission was identified as a prognostic factor for mortality from HCAP, as previously reported[23].

We also found treatment failure of initial antibiotics to be associated with mortality. As addressed previously in the guidelines[1], several factors relate to failure to improve, which include bacterial, host, and therapeutic factors. Because MDR pathogens are more common in HCAP than CAP and inappropriate initial antimicrobial therapy increases mortality[24, 25], broad-spectrum coverage as empirical therapy has been recommended[1]. In the present study, the frequency of MDR pathogen infections was 9.8%, which was higher than that of CAP in our hospital[5], indicating that patients requiring broad-spectrum therapy more frequently have HCAP than CAP. Further, MDR pathogens accounted for 21.3% of non-survivors, which suggests MDR pathogens to be important therapeutic targets to mitigate negative outcomes of HCAP. Falcone *et al*[26] showed that empirical broad-spectrum therapy was associated with improved outcome in patients with HCAP. However, Attridge *et al*[27] reported that guideline-concordant HCAP therapy is not associated with improved survival compared with guideline-concordant CAP therapy, in nonsevere HCAP. This result may be due to the high prevalence of culture-negative infections, which can be treated effectively following a CAP regimen[28, 29], or to a low local prevalence of resistant pathogens[30]. Unfortunately, because none of our patients had received anti-MRSA therapy, we could not assess the relation between HCAP guideline-concordant therapy[1] and outcome. In addition, we found that there were still significant numbers of traditional CAP pathogens isolated in HCAP patients, as reported previously[31, 32]; however, we could not statistically prove the efficacy of CAP treatment on mortality in HCAP. Further studies are needed to determine appropriate antibiotic selection.

Early use of NIs can reduce development of complications such as pneumonia[33], and current Center for Disease Control guidelines recommend NIs for hospitalized patients with influenza virus infection[34]. We could not study the efficacy of NIs on influenza virus infection because of the small number of patients, and further studies are needed to clarify this matter in HCAP. In addition, Rosón *et al*[24] reported that factors other than inappropriate antibiotic selection are frequent causes of treatment failure and suggested that the capacity of antibiotic therapy to further reduce mortality may be limited[24]. In our study, 29.9% of patients with disease progression after initial antibiotic therapy had received appropriate therapy, and 5 of 10 non-survivors with MDR pathogen infection had received appropriate therapy. Similar studies have also been reported[35, 36], and these findings suggest that treatment strategies for HCAP other than antibiotic selection are also required. HCAP patients are often functionally disabled, and patient-related factors including functional status may be needed in the analysis of prognostic factors, which was difficult in the present study due to its retrospective nature.

We analyzed patients meeting the current HCAP criteria[1]. Because the risk of infection by an MDR pathogen is not equivalent for each criterion defining HCAP[9], the frequency of MDR pathogens may differ in accordance with the frequency of patients with each criterion. Differences in epidemiology of drug-resistant pathogens and healthcare and social health insurance systems among countries and regions should be taken into account. Park *et al*[9] reported a poor prediction of potentially drug-resistant pathogens in Korea, using the current HCAP criteria. In 2011, the Japanese Respiratory Society proposed a modified concept of HCAP called "nursing

and healthcare-associated pneumonia", considering the epidemiological and social environmental situations in Japan[37]. Ishida *et al*[38] revealed the usefulness of the guidelines in a prospective manner. To define better strategies and to mitigate negative outcomes from HCAP, further studies are needed to identify predictive factors of MDR pathogens and prognostic factors.

The present study has several limitations. First, because it is a retrospective, observational, single-center study, the level of confidence is reduced, and the results may not be applicable in other settings. Second, a complete diagnostic workup to determine etiology was not possible in every patient. Third, we did not use PCR assay methods in the etiological diagnosis. Although PCR techniques are more labor intensive and technically demanding and require specialized laboratory equipment, PCR is sensitive, and some cases of influenza or other virus, infection may have been missed.

In conclusion, in the patients with HCAP, the most frequent microbial agents were *S. pneumoniae*, *P. aeruginosa*, and influenza virus. Disease severity and treatment failure of initial antibiotics were independent risk factors for mortality from HCAP. MDR pathogens are important therapeutic targets to mitigate negative results, and treatment strategies other than antibiotic selection are also required to reduce treatment failure.

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Conflict of interest

The authors have declared no conflict of interest.

References

1) American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;**171**:388-416.
2) Kollef MH, Shorr A, Tabak YP, *et al*. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest*. 2005;**128**:3854-3862.
3) Chalmers JD, Taylor JK, Singanayagam A, *et al*. Epidemiology, antibiotic therapy, and clinical outcomes in health care-associated pneumonia: a UK cohort study. *Clin Infect Dis*. 2011;**53**:107-113.
4) Carratala J, Mykietiuk A, Fernandez-Sabe N, *et al*. Health care-associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. *Arch Intern Med*. 2007;**167**:1393-1399.
5) Ishiguro T, Takayanagi N, Yamaguchi S, *et al*. Etiology and factors contributing to the severity and mortality of community-acquired pneumonia. *Intern Med*. 2013;**52**:317-324.
6) Mandell LA, Wunderink RG, Anzueto A, *et al*. Infectious Disease Society of America / American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;**44 Suppl 2**:S27-S72.
7) Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev*. 2001;**14**:933-951.
8) Dennesen PJ, van der Ven AJ, Kessels AG, *et al*. Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2001;**163**:1371-1375.

9) Park SC, Kang YA, Park BH, *et al*. Poor prediction of potentially drug-resistant pathogens using current criteria of health care-associated pneumonia. *Respir Med*. 2012;**106**:1311-1319.
10) Giannella M, Pinilla B, Capdevila JA, *et al*. Pneumonia treated in the internal medicine department: focus on healthcare-associated pneumonia. *Clin Microbiol Infect*. 2012;**18**:786-794.
11) Shindo Y, Sato S, Maruyama E, *et al*. Health-care-associated pneumonia among hospitalized patients in a Japanese community hospital. *Chest*. 2009;**135**:633-640.
12) Garcia-Vidal C, Viasus D, Roset A, *et al*. Low incidence of multidrug-resistant organisms in patients with healthcare-associated pneumonia requiring hospitalization. *Clin Microbiol Infect*. 2011;**17**:1659-1665.
13) Marcos MA, Esperatti M, Torres A. Viral pneumonia. *Curr Opin Infect Dis*. 2009;**22**:143-147.
14) Oliveira EC, Marik PE, Colice G. Influenza pneumonia: a descriptive study. *Chest*. 2001;**119**:1717-1723.
15) Jennings LC, Anderson TP, Beynon KA, *et al*. Incidence and characteristics of viral community-acquired pneumonia in adults. *Thorax*. 2008;**63**:42-48.
16) Johnstone J, Majumdar SR, Fox JD, *et al*. Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. *Chest*. 2008;**134**:1141-1148.
17) Templeton KE, Scheltinga SA, van den Eeden WC, *et al*. Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin Infect Dis*. 2005;**41**:345-351.
18) Maruyama T, Niederman MS, Kobayashi T, *et al*. A prospective comparison of nursing home-acquired pneumonia with hospital-acquired pneumonia in non-intubated elderly. *Respir Med*. 2008;**102**:1287-1295.
19) Choi SH, Hong SB, Ko GB, *et al*. Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med*. 2012;**186**:325-332.
20) Fine MJ, Auble TE, Yealy DM, *et al*. A prediction rule to identify low-risk patients with community acquired pneumonia. *N Engl J Med*. 1997;**336**:243-250.
21) Lim WS, van der Eerden MM, Laing R, *et al*. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;**58**:377-382.
22) Carrabba M, Zarantonello M, Bonara P, *et al*. Severity assessment of healthcare-associated pneumonia and pneumonia in immunosuppression. *Eur Respir J*. 2012;**40**:1201-1210.
23) Park HK, Song JU, Um SW, *et al*. Clinical characteristics of health care-associated pneumonia in a Korean teaching hospital. *Respir Med*. 2010;**104**:1729-1735.
24) Roson B, Carratala J, Fernandez-Sabe N, *et al*. Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. *Arch Intern Med*. 2004;**164**:502-508.
25) Micek ST, Reichley RM, Kollef MH. Healthcare-associated pneumonia (HCAP) empiric antibiotics targeting methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa predict optimal outcome. *Medicine (Baltimore)*. 2011;**90**:390-395.
26) Falcone M, Corrao S, Licata G, *et al*. Clinical impact of broad-spectrum empirical antibiotic therapy in patients with healthcare-associated pneumonia: a multicenter interventional study. *Intern Emerg Med*. 2012;**7**:523-531.
27) Attridge RT, Frei CR, Restrepo MI, *et al*. Guideline-concordant therapy and outcomes in healthcare-associated pneumonia. *Eur Respir J*. 2011;**38**:878-887.
28) Labelle AJ, Arnold H, Reichley RM, *et al*. A comparison of culture-positive and culture-negative health-care-associated pneumonia. *Chest*. 2010;**137**:1130-1137.
29) Schlueter M, James C, Dominguez A, *et al*. Practice patterns for antibiotic de-escalation in culture-negative healthcare-associated pneumonia. *Infection*. 2010;**38**:357-362.
30) Zilberberg MD, Shorr AF. Healthcare-associated pneumonia: the state of evidence to date. *Curr Opin Pulm Med*. 2011;**17**:142-147.
31) Schreiber MP, Chan CM, Shorr AF. Resistant pathogens in non-nosocomial pneumonia and respiratory failure: is it time to refine the definition of health-care-associated pneumonia? *Chest*. 2010;**137**:1283-1288.

32) Shorr AF, Zilberberg MD, Micek ST, *et al*. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med*. 2008;**168**:2205-2210.
33) Yu H, Liao Q, Yuan Y, *et al*. Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China. *BMJ*. 2010;**341**:c4779.
34) Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians (Internet). (accessed 2011 May 8) http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.
35) Musher DM, Alexandraki I, Graviss EA, *et al*. Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. *Medicine* (*Baltimore*). 2000;**79**:210-221.
36) Arancibia F, Bauer TT, Ewig S, *et al*. Community-acquired pneumonia due to gram-negative bacteria and pseudomonas aeruginosa: incidence, risk, and prognosis. *Arch Intern Med*. 2002;**162**:1849-1858.
37) The Japanese Respiratory Society. *Nursing and healthcare-associated pneumonia*. Tokyo: The Japanese Respiratory Society; 2011. (in Japanese).
38) Ishida T, Tachibana H, Ito A, *et al*. Clinical characteristics of nursing and healthcare-associated pneumonia: a Japanese variant of healthcare-associated pneumonia. *Intern Med*. 2012;**51**:2537-2544.

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