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지역 사회 폐렴의 차이 분석

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의 학 과

성길명

2013년 2월

Healthcare-associated pneumonia among hospitalized
patients : Is it different from community acquired
pneumonia?

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ABSTRACT

Background: The increasing number of outpatients with MDR pathogens has led to a new category of pneumonia, termed healthcare-associated pneumonia (HCAP). We determined the differences in etiology and outcomes between patients with HCAP and those with community-acquired pneumonia (CAP) to clarify the risk factors for HCAP mortality.

Methods: A retrospective study comparing patients with HCAP and CAP at Jeju National University Hospital. The primary outcome was 30-day mortality.

Results: A total of 483 patients (208 patients HCAP; 275 patients with CAP) were evaluated. Patients with HCAP were older than those with CAP (median, 74 years; IQR, 65–81 vs. median, 69 years; IQR, 52–78; $p < 0.0001$). *Streptococcus pneumoniae* was the major pathogen in both groups, and MDR pathogens were isolated more frequently from patients with HCAP than with CAP (18.8% vs. 4.9%; $p < 0.0001$). Initial pneumonia severity was greater in patients with HCAP than with CAP. The total 30-day mortality rate was 9.9% and was higher in patients with HCAP based on univariate analysis (16.3% vs. 5.1%; odds ratio (OR), 3.64; 95% confidence interval (CI), 1.90–6.99; $p < 0.0001$). After adjusting for age, sex, comorbidities, and initial severity, the association between HCAP and 30-day mortality became non-significant (OR, 1.98; 95% CI, 0.94–4.18; $p = 0.167$).

Conclusions: HCAP was a common cause of hospital admissions and was associated with a high mortality rate. This increased mortality was related primarily to age and initial clinical vital signs, rather than combination antibiotic therapy or type of pneumonia.

Introduction

Pneumonia is typically classified as community-acquired (CAP), hospital-acquired (HAP), or ventilator-associated (VAP). However, over the past few decades, some patients presenting as outpatients with pneumonia have been infected with multidrug-resistant (MDR) pathogens such as *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, and extended-spectrum β -lactamase (ESBL) producing Enterobacteriaceae¹. The potential involvement of these MDR pathogens has led to a new category of pneumonia, termed healthcare-associated pneumonia (HCAP). In 2005, the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) published the first guidelines for managing adults with HCAP². In these guidelines, HCAP is included in the spectrum of HAP and VAP, and all patients with HCAP require therapy with dual antipseudomonal antibiotics plus linezolid or vancomycin for MDR pathogens.

Although the new pneumonia classification system has been helpful for determining empirical antibiotic strategies, it is not without its disadvantages. First, because of a lack of large-scale prospective studies and limited epidemiological data, the clinical outcomes of the 2005 ATS/IDSA guidelines are still under discussion. Not all MDR pathogens are associated with all risk factors. In addition, risk factors for an MDR pathogen infection do not preclude the development of pneumonia caused by the typical CAP pathogens³.

Methods

This was a retrospective observational study conducted at Jeju National University Hospital, a 500-bed teaching hospital in Jeju, Republic of Korea, between January 2010 and December 2011. All consecutive patients with pneumonia admitted to the hospital through the emergency or outpatient department were eligible. One of the investigators (GM Seong) reviewed all 1,754 patients hospitalized at the Department of Respiratory and Allergy during the 2-year period to identify appropriate patients. Patients with HAP, those on a home

mechanical ventilator, patients referred after antibiotic administration, and patients with HIV infection or organ transplantation were excluded. We considered that patients who fulfilled the HCAP criteria but developed pneumonia within 10 days after discharge as having developed HAP. We classified study patients into CAP and HCAP groups, and compared clinical characteristics, severity, pathogen distribution, and outcomes between the two groups. Our study protocol was approved by the Institutional Review Board of Jeju National University Hospital.

Definition of pneumonia

Patients with pneumonia were defined as those presenting with a new radiographic infiltrate and at least two of the following symptoms or signs: cough, sputum production, hemoptysis, dyspnea, fever, pleuritic chest pain, or signs consistent with pneumonia on physical examination⁴. HCAP and CAP were defined according to the ATS/IDSA guidelines^{2,5}. The HCAP group included patients with any of the following: (1) hospitalization for ≥ 2 days during the preceding 90 days; (2) residence in a nursing home or long-term care facility; (3) recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days before entering the study; (4) long-term dialysis, including hemodialysis and peritoneal dialysis, within 30 days of entering the study. The diagnosis and type of pneumonia were verified twice from the medical records by one of the investigators (GM Seong or MO Kim).

Microbiological evaluation

Recommended initial microbiological investigations were sputum and blood cultures, *Legionella* and pneumococcal urine antigen testing, an antibody titer for *Mycoplasma pneumoniae*, and acid-fast bacterial (AFB) stains and cultures in selected patients. Specimens acceptable for positive culture results included sputum, tracheal aspirate, bronchoscopic bronchoalveolar lavage fluid, and blood. Blood culture results were accepted if the same

microorganism was also identified in a respiratory specimen or if no other source for the positive blood culture was identified. Additionally, a positive *Legionella* urine antigen result, an antibody titer for an atypical pathogen that changed to 4-fold or converted to positive, and a positive polymerase chain reaction (PCR) for *Mycobacterium tuberculosis* were considered to indicate etiological pathogens.

Antibiotic therapy was classified as being inappropriate if the initially prescribed antibiotics were not active against the identified pathogens, based on *in vitro* susceptibility testing. Exceptionally, atypical pathogens such as *M. pneumoniae*, *Chlamydia* species, and *Legionella* species were considered fully susceptible to fluoroquinolones or macrolides, and *M. tuberculosis* was excluded from being judged appropriately, because it requires a special antibiotic regimen.

Severity evaluation and outcomes

All patients were assessed for risk at admission using the Pneumonia Severity Index (PSI) and CURB-65 scores^{6,7}. Patients were followed for 30 days from the date of admission. We recorded the 30-day mortality and the need for admission to the intensive care unit, mechanical ventilation, and/or vasopressor support. Initial treatment failure was defined as death during initial treatment or a change from the initial antibiotic to another drug after 48 h because of clinical instability (e.g., lack of response, worsening of fever, or requirement for mechanical ventilation or vasopressors).

Statistical analysis

All statistical analyses were performed using PASW Statistics 17 (SPSS, Inc., Chicago, IL, USA). A level of $\alpha < 0.05$ was considered to indicate statistical significance. The χ -squared test was used to compare categorical variables. Continuous variables were analyzed using Student's *t*-test or the Mann-Whitney *U* test. Multivariate logistic regression analysis was

performed to identify independent risk factors associated with 30-day mortality, as measured by the adjusted odds ratio (AOR) with 95% confidence intervals (CIs). The 30-day mortality was the dependent variable, and all potential risk factors with p-values < 0.2 in the univariate analysis were independent variables in the multivariate logistic regression model.

Results

Patients

A total of 483 patients were evaluated (208 patients with HCAP and 275 with CAP) (Figure 1). Most of these patients were admitted due to a recent admission (54.3%) or residence in a nursing home (48.1%) (including overlapping cases). Eighty-four patients (40.4%) had more than two risk factors. The demographic and baseline clinical characteristics of the patients with HCAP and CAP are presented in Table 1. Patients with HCAP were older and had a lower body mass index than patients with CAP. No gender differences were observed between the groups, but comorbidities such as cancer, congestive heart failure, cerebrovascular disease, and dementia occurred more frequently in patients with HCAP.

Figure 1. Flow diagram of the study population.

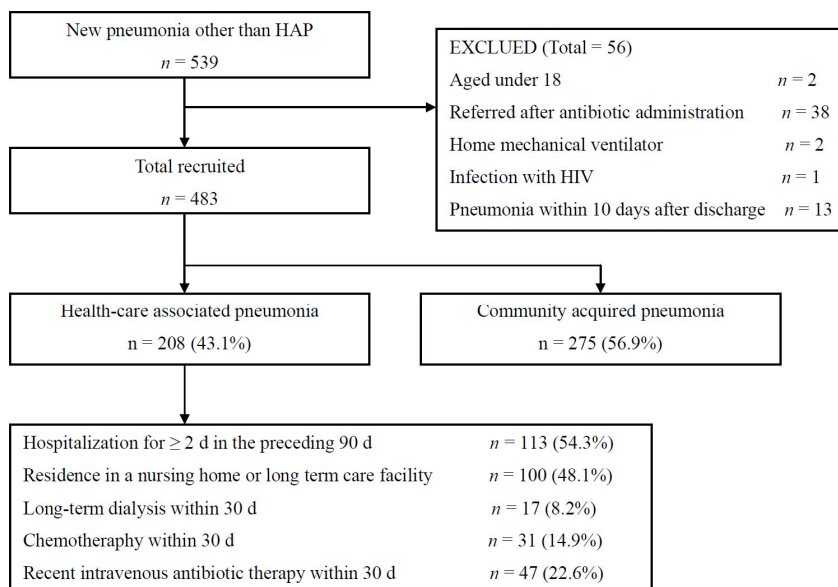


Table 1. Baseline demographics and illness severity*

Variable	HCAP Patients (n = 208)	CAP Patients (n = 275)	p-value
Male gender	133 (63.9)	153 (55.6)	0.066
Age, years	74 (65–81)	69 (52–78)	<0.0001
Age > 65 years	157 (75.5)	157 (57.1)	<0.0001
BMI, kg/m ²	21.7 (18.6–23.4)	21.9 (19.5–24.7)	0.01
Hospital stay, days	9 (6–15)	7 (5–10)	<0.0001
Comorbidities			
Malignancy	63(30.3)	31(11.3)	<0.0001
Chronic lung disease	39(18.8)	52 (18.9)	0.965
Congestive heart failure	21 (10.1)	13 (4.7)	0.022
Chronic kidney disease	25 (12.0)	17 (6.2)	0.024
Chronic liver disease	13 (6.3)	14 (5.1)	0.583
Cerebrovascular disease	73 (35.1)	50 (18.2)	<0.0001
Dementia	58 (27.9)	13 (4.7)	<0.0001
Diabetes mellitus	48 (23.1)	44 (16.0)	0.05
Clinical parameters			
Confusion	49 (23.6)	25 (9.1)	<0.0001
Systolic BP <90 mm Hg or Diastolic BP ≤60 mm Hg	69 (33.2)	55 (20.0)	0.001
Respiratory rate ≥30 breaths/min	35 (16.8)	44 (16.0)	0.808
SpO ₂ ≤90% or PaO ₂ ≤60 mm Hg	100 (48.1)	99 (36.0)	0.008
Laboratory findings			
pH <7.35†	16/176 (9.1)	17/183 (9.3)	0.948
BUN >19 mg/dL	123 (59.1)	99 (36.0)	<0.0001
Na <130 mmol/L	19 (9.1)	8 (2.9)	0.003
Glucose ≥250 mg/dL	17 (8.2)	15 (5.5)	0.234
Hematocrit <30%	59 (28.4)	22 (8.0)	<0.0001
ESR, mm/h	68 (44–101)	61 (39–96)	0.467
CRP, mg/dL	12.04 (6.31–19.98)	10.51 (4.32–18.63)	0.063
Procalcitonin	0.43 (0.13–1.91)	0.16 (0.09–0.75)	0.130
Probable aspiration pneumonia	80 (38.5)	26 (9.5)	<0.0001
Tube feeding	29 (13.9)	8 (2.9)	<0.0001

Severe sepsis	81 (38.9)	56 (20.4)	<0.0001
ICU admission	61 (29.3)	36 (13.1)	<0.0001
Pneumonia Severity Index score	112 (100–143)	82 (57–111)	<0.0001
CURB-65	2 (1–3)	1 (0–2)	<0.0001

HCAP, healthcare-associated pneumonia; CAP, community-acquired pneumonia; BMI, body mass index

* Data are presented as number (%), mean \pm standard deviation, or median (25th–75th percentile).

† Initial arterial blood gas analysis was performed in 359 (74.3%) of the study patients.

Microbiology and antibiotic treatments

A positive microbiological diagnosis was made in 51.3% of the patients with HCAP compared with 39.2% of the patients with CAP ($p = 0.009$). The frequencies of the organisms isolated in both groups are shown in Table 2. *Streptococcus pneumoniae* was the major pathogen in both groups, and *S. aureus*, *P. aeruginosa*, and polymicrobial pathogens were isolated more frequently from patients with HCAP than from those with CAP. *Mycobacterium tuberculosis* was identified at an overall frequency of 6.4%, with no significant group difference ($p = 0.65$).

After adjusting for age, comorbidities, and the HCAP risk group, the use of antibiotics within 90 days and tube feeding were significantly correlated with the occurrence of MDR pathogens (AOR, 8.03; 95% CI, 2.46–26.21; $p = 0.001$ and AOR, 9.42; 95% CI, 3.40–26.13; $p < 0.0001$, respectively).

The most frequently prescribed initial antibiotic regimen was antipseudomonal β -lactam plus fluoroquinolone (48.6%; e.g., piperacillin/tazobactam 4.5 g q8h plus levofloxacin 750 mg q24h) for HCAP and third and fourth-generation cephalosporins and macrolides (63.3%; e.g., ceftriaxone 2 g q24h plus azithromycin 500 mg q24h) for CAP (data not shown). In addition, vancomycin was used in 15 patients with HCAP (7.2%) and eight patients with CAP (2.9%).

Table 2. Microbes identified in the HCAP and CAP groups*

Microbe	HCAP Patients (n = 199)†	CAP Patients (n = 268)†	p-value
Gram-positive pathogens	67 (33.7)	59 (22.0)	0.005
<i>Streptococcus pneumoniae</i>	34 (17.1)	44 (16.4)	0.85
<i>Staphylococcus aureus</i>	32 (16.1)	10 (3.7)	<0.0001
MSSA	16 (8.0)	7 (2.6)	0.007
MRSA	16 (8.0)	3 (1.1)	0.0001
<i>Streptococci other than S. pneumonia</i>	1 (0.5)	5 (1.9)	0.2
Gram-negative pathogens	29 (14.6)	19 (7.1)	0.008
<i>Pseudomonas species</i>	19 (9.5)	10 (3.7)	0.01
<i>Klebsiella species</i>	4 (2.0)	6 (2.2)	0.87
ESBLs	2 (1.0)	1 (0.4)	
<i>Escherichia coli</i>	0	0	
ESBLs	0	0	
<i>Moraxella catarrhalis</i>	2 (1.0)	1 (0.4)	
<i>Haemophilus influenzae</i>	0	1 (0.4)	
<i>Bordetella pertussis</i>	0	1 (0.4)	
<i>Enterobacter species</i>	2 (1.0)	0	
<i>Proteus mirabilis</i>	0	0	
Acinetobacter species	1 (0.5)	0	
<i>Stenotrophomonas maltophilia</i>	0	0	
<i>Burkholderia cepacia</i>	1 (0.5)	0	
Other Gram-negative bacteria‡	1 (0.5)	0	
Atypical pathogens			
<i>Chlamydia pneumoniae</i>	0	0	
<i>Mycoplasma pneumoniae</i>	0	7 (2.6)	0.02
<i>Legionella pneumophila</i>	0	0	
Influenza virus	2 (1.0)	4 (1.5)	0.65
<i>Mycobacterium tuberculosis</i>	12 (6.0)	19 (7.1)	0.65
Nontuberculous mycobacteria	0	1 (0.4)	
<i>Pneumocystis jiroveci</i>	1 (0.5)	0	
Aspergillosis species	1 (0.5)	0	
Anaerobes	0	0	

Polymicrobial pathogens	10/102 (9.8)	4/105 (3.8)	0.009
MDR pathogens	36 (18.1)	13 (4.9)	<0.0001
No pathogen identified	97 (48.7)	163 (60.8)	0.009

*Data are presented as number (%).

†Nine HCAP and seven CAP patients were excluded from the analysis because of missing data.

‡ Unidentified Gram-negative pathogen in the blood culture.

Severity of pneumonia and clinical outcomes

As shown Table 1, initial severities as measured by the PSI and CURB-65 were significantly higher in patients with HCAP than in those with CAP, and a probable case of aspiration pneumonia was more frequent in patients with HCAP.

The overall 30-day mortality rate was 9.9%. In a univariate analysis, HCAP was associated with not only an increased 30-day mortality rate (HCAP, 16.3%; CAP, 5.1%; $p < 0.0001$) but also an increased rate of mechanical ventilation or vasopressor support (HCAP, 20.7%; CAP, 9.5%; $p < 0.0001$). The age distribution was one of the strongest risk factors for mortality. After excluding six unusually young cases (extreme values), the minimum age in the HCAP group was 42 years. Thus, we limited our study patients to those aged ≥ 42 years to reduce the effect of age. Forty-nine patients (6 with HCAP and 43 with CAP) were excluded, and there were no 30-day mortalities among these patients. In this limited study population, the univariate OR for HCAP and 30-day mortality was 3.15 (95% CI, 1.64–6.06; $p < 0.0001$). However, after adjusting for age, sex, comorbidities, initial severity (CURB-65 score) and use of antipseudomonal antibiotics, the association between HCAP and the 30-day mortality rate became non-significant (OR, 1.98; 95% CI, 0.94 – 4.18; $p = 0.167$) (table 3). The Hosmer–Lemeshow test indicated a good fit for both models ($p > 0.05$).

Inappropriate initial antimicrobial treatment was significantly higher in patients with HCAP than in those with CAP ($p = 0.047$), but it did not correlate with 30-day mortality ($p = 0.293$). Among patients with HCAP, the use of antipseudomonal antibiotics as an initial therapy was not associated with a decrease in 30-day mortality in either the univariate ($p = 0.09$) or

multivariate analysis (AOR, 1.67; 95% CI, 0.72–3.90; $p = 0.24$). Of the HCAP risk factors, only residence in a nursing home was independently associated with an increase in 30-day mortality (AOR, 4.46; 95% CI, 1.37–13.90; $p = 0.013$).

Table 3. Multivariate analysis of the predictors of 30 day mortality

	Odds ratio	95% CI	p-value
Age	1.03	0.98 – 1.07	0.237
Male	1.70	0.80 – 3.59	0.167
HCAP	1.98	0.94 – 4.18	0.074
Malignancy	1.64	0.71 – 3.84	0.250
Chronic lung disease	0.21	0.04 – 1.03	0.054
Congestive heart failure	2.08	0.67 – 6.41	0.203
Chronic kidney disease	0.41	0.81 – 2.10	0.286
Chronic liver disease	0.94	0.19 – 4.70	0.074
Cerebrovascular disease	0.81	0.37 – 1.80	0.611
CURB-65 stage			
Low (0~1)	1.00		
Intermediate (2)	3.06	0.82 – 11.43	0.096
High (3~5)	12.92	3.84 – 43.48	<0.001
Tube feeding	1.58	0.50 – 4.99	0.437
Use of Antipseudomonal antibiotics	0.42	0.08 – 2.25	0.311

Discussion

Healthcare-associated pneumonia is a new category of pneumonia with potential involvement of MDR pathogens and is distinct from CAP. The 2005 IDSA/ATS guidelines concluded that all patients with HCAP are at risk for MDR pathogen infection. Thus, broad spectrum therapy with triple antibiotics is recommended for all patients with HCAP². Despite these recommendations, the evidence specifically related to patients with HCAP is weak, and no randomized controlled trials have been conducted. Of the 294 references cited by the ATS/IDSA guidelines, only seven originally related to HCAP, and these were about nursing home-associated pneumonia⁸⁻¹⁰. Kollef et al.¹ published a large retrospective HCAP data series in the U.S., shortly after the guidelines were introduced. Among patients with HCAP, about 50% had MRSA or *Pseudomonas aeruginosa*, and overall mortality was similar to that of patients with HAP (19.8% and 18.8%, respectively). These findings were consistent in several subsequent U.S. studies¹¹⁻¹⁴. However, many disagreements have occurred among physicians, and recently reported studies from countries other than the U.S. have suggested that the frequency of MDR pathogens is more similar to that with CAP¹⁵⁻²⁰.

Our study aimed to determine the differences in etiology and outcomes between patients with HCAP and those with CAP, and to clarify antibiotic strategies for HCAP in a tertiary teaching hospital in Jeju, Korea. HCAP accounted for 43.1% of hospitalized patients with pneumonia in the present study, and the incidence of HCAP was higher than that in previous studies (17.3–38.0%)^{1,15,21,22}. The definition of HCAP was widely variable in previous studies, and some studies included only culture-positive patients. Our analysis included only hospitalized pneumonia cases and studies performed at a referral hospital. Because of the retrospective nature of this study, the true incidence of HCAP cannot be estimated. However, it is of greater importance that more than one-third of hospitalized pneumonia cases may have MDR pathogens.

In the present study, the overall 30-day mortality rate was 9.9%. As in previous studies, the

mortality rate of patients with HCAP was three times that of patients with CAP. However, no relationship between HCAP and mortality was observed after adjustments for confounding variables. Investigating the underlying reasons for the increased mortality was complicated for several reasons. First, patients with HCAP were older and had more frequent comorbidities. As these two factors are powerful prognostic factors for pneumonia, other factors would be easily diluted in a retrospective study. In addition, it is uncertain whether MDR pathogens and inappropriate antibiotics were directly associated with higher mortality in patients with HCAP. Previous data on critically ill patients have shown that inappropriate antibiotic treatment is related to higher mortality²³⁻²⁵. However, outcomes and initial extended antibiotics are not simply defined in patients with HCAP. Rello et al.²⁶ reported that pneumococcal HCAP results in excess mortality that is independent of bacterial susceptibility. These differences in outcomes were probably due to differences in age, comorbidities, and ICU admission criteria, rather than therapeutic decisions. Recent studies from the U.S.²⁷ and Canada²⁸ have suggested that therapy consistent with the 2005 ATS/IDSA guidelines fails to decrease mortality and in some cases, tends to correlate with increased mortality.

About 40% of the patients in the HCAP group had more than two risk factors. It is unclear whether each healthcare environment had the same risk for MDR pathogens, or whether there are multiple risk factors for MDR pathogens. According to the current definition, HCAP is a distillation of multiple risk factors; thus, each patient must be considered individually, particularly with regard to performance status. For example, the risk for infection with MDR pathogens in a nursing home resident who has dementia but maintains daily self-care activities is different from the risk in a patient who is in a vegetative state with a tracheostomy and a feeding tube.

The ATS-IDSA guidelines for the empirical treatment of HCAP indicate that MRSA should be treated with either vancomycin or linezolid^{2,19}. However, the impact of this

recommendation on clinical outcomes, including mortality, is limited, and the prevalence of MRSA varies^{29,30}. In the present study, MRSA was identified in 7.7% of the patients with HCAP, and 7.2% of the patients with HCAP were initially prescribed vancomycin. We could not analyze clinical outcomes and vancomycin use because the incidence of MRSA and frequency of vancomycin administration were too low.

Mycobacterium tuberculosis was isolated from 5.8% of patients with HCAP and 6.9% of patients with CAP. In most previous HCAP studies, *M. tuberculosis* was not considered a major pathogen and was not evaluated. According to our data, *M. tuberculosis* is not rare in patients with HCAP, and AFB staining and cultures should be considered in the initial diagnostic work-up in *M. tuberculosis*-endemic areas^{31,32}.

Although study did not establish a clear guideline to choose antibiotics, it is important to know local epidemiologic data.

We found causative microorganisms in hospitalized pneumonia cases except those of HAP. Significantly more *Pseudomonas* species were identified in the HCAP group than in the CAP group, yet fewer than 10% of the *Pseudomonas* pneumonia cases occurred in the HCAP group. This suggests that the use of double or triple broad-spectrum antibiotics may not be justified, although we did not seek to establish clear guidelines for choosing antibiotics in the present study. After adjusting for potential confounders, the 30-day mortality rate was not significantly higher in the HCAP group compared with the CAP group. The observed higher mortality in patients with HCAP may be attributable mainly to the age of the patient and the initial clinical severity of the disease. While an unverified, broad definition of HCAP may obscure the importance of healthcare-associated MDR infections, it is nevertheless important to understand local epidemiological data on MDR infections. Unfortunately, few studies have evaluated HCAP epidemiology in Korea^{33,34}.

Our study had some limitations that warrant consideration. First, because this was a retrospective study, unintentional data loss might have influenced the HCAP classification,

despite our careful review of medications and hospitalization. We did not collect data on premonitory performance status or treatment limitations such as do not resuscitate orders. Therefore, we could not evaluate how performance status and treatment restrictions might have influenced clinical outcomes. Second, there are some limitations regarding available laboratory data. *Haemophilus influenzae* is a major pathogen of adult pneumonia, but reported culture-positive results were extremely rare. No follow-up antibody titer tests were performed in any of the suspected *M. pneumoniae* patients. Third, consideration of special conditions such as tracheostomy or a feeding tube *in situ* was lacking.

In conclusion, HCAP was a common cause of hospital admissions and was associated with a high mortality rate. However, the higher mortality rate in patients with HCAP was not related to MDR pathogens. Thus, broad-spectrum antibiotics should be used with caution in these patients. The regional variations in the incidence and microbiology of HCAP emphasize the importance of understanding the local epidemiology. Furthermore, heterogeneous HCAP data may be confusing, and the HCAP concept should be carefully defined. A well-designed substantial study is imminent.

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