# The definition of Healthcare-associated pneumonia (HCAP) is insufficient for medical environment in Japan: A comparison of HCAP and Nursing and Healthcare-associated pneumonia (NHCAP).

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**ABSTRACT**

Healthcare-associated pneumonia (HCAP) is a new concept of pneumonia, which was proposed in ATS/IDSA guidelines. The guidelines explain that HCAP patients should be treated with broad-spectrum antimicrobial drugs directed at multidrug-resistant (MDR)-pathogens. However, in Japan, there are many elderly people who received an in-home care service. They seemed to be consistent with the concept of HCAP, but they didn't meet the definition of HCAP. Therefore, the Japanese Respiratory Society modified the definition of HCAP according to medical environmental in Japan. We retrospectively observed HCAP patients and nursing and healthcare-associated pneumonia (NHCAP) patients who were hospitalized between 24 months at the Japanese Red Cross Nagasaki Genbaku Hospital (Nagasaki, Japan). Patient background, disease severity, identified pathogens, initial antibiotic regimens, and outcomes were compared. A total of 108 patients (77 HCAP and 31 NHCAP except HCAP patients) were evaluated. Of NHCAP except HCAP patients, 27 (87.1%) were over 3 in ECOG PS score. There were almost no significantly differences between two groups in the characteristics, pneumonia severity, identified bacteria, initial antibiotic regimens, and response rate of initial antibiotic therapy. Although the in-hospital mortality of HCAP patients and NHCAP except HCAP patients was 9.1% and 19.4%, respectively, this difference did not reach

statistical significance ($P$>0.05). Our study suggested that, in the criteria of HCAP, some Japanese patients, who were consistent with the concept of HCAP, were classified into community-acquired pneumonia. Therefore, there is a need to change the definition of HCAP according to medical environment in Japan.

**Key words:** pathogens, antibiotics, pneumonia severity index, CURB-65, mortality

## INTRODUCTION

Healthcare-associated pneumonia (HCAP) is a relatively new concept which was recently documented in the 2005 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) hospital-acquired pneumonia (HAP) guidelines [1]. The recent guidelines recommend treating HCAP patients with broad-spectrum antimicrobial drugs, as is presently done for patients at risk of multidrug-resistant pneumonia including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.

Since the publication of the guidelines, preliminary studies have reported that HCAP, particularly in form of MRSA and *Pseudomonas aeruginosa*, is frequently observed [2, 3]. Additionally, the mortality rate of HCAP was found to be higher, compared to that of CAP [2, 3]. However, some reviews [4, 5] reported that HCAP is a heterogeneous disease and cast doubt on the notion that all patients with HCAP must receive empiric therapy with a multidrug regimen directed against multidrug-resistant (MDR)-pathogens.

These results suggested that the actual state of HCAP was different by medical environment. In Japan, definitions of hospital are different from the United States (e.g. in Japan, there are many long-term care hospitals which is classified as a nursing home

in the United States). By Japanese national system of care insurance, there are many elderly people who receive an in-home care service, and they seem to be consistent with the concept of HCAP; but they didn't meet the definition of HCAP.

In Japan, how to treat the HCAP patients has been very important issue because of it aging society. The United Nations reported that the percentage of people over 60 years in Japan in 2011 was 37.7% [6]. It is much higher than that in United States (17.6%) and in United Kingdom (27.5%). Therefore, the Japanese Respiratory Society (JRS) modified the definition of HCAP according to medical environment in Japan, and they announced the nursing and healthcare-associated pneumonia (NHCAP) guidelines [7]. However, there has been no study on the modified definition.

The purpose of this study was to reveal the need to change the definition of HCAP according to each country's medical environment. In this study, HCAP and NHCAP except HCAP were compared for patient background, disease severity, identified pathogens, initial antibiotic regimens, and in-hospital mortality.

## Methods

### Study design and patient population

We conducted a retrospective observational study of pneumonia patients (excluding those with HAP) who were hospitalized at the Japanese Red Cross Nagasaki Genbaku Hospital between January 1, 2007 and October 31, 2010. The facility is a community hospital containing 360 beds, located in Nagasaki City, Nagasaki, Japan. We compared baseline characteristics, disease severity, distribution of pathogens, antibiotic regimens, outcomes, and performance status (PS), as defined by the European cooperative oncology group (ECOG) [8]. We adhered to the Japanese ethical guidelines for epidemiologic studies and the protocol for this study was approved by the ethics committees of the Japanese Red Cross Nagasaki Genbaku Hospital.

### Definitions

HCAP was defined according to the ATS/IDSA guidelines [1]. In the guidelines, HCAP was defined as a diagnosis of pneumonia in patients admitted to the hospital who met at least one of the following criteria: (1) hospitalization for 2 days or more in the preceding 90 days; (2) residence in a nursing home or extended care facility; (3) home infusion therapy (including antibiotics); (4) chronic dialysis within 30 days; (5) home wound care; (6) family member with an MDR pathogen. NHCAP was defined

according to the JRS guidelines [7]. Patients are diagnosed with NHCAP when they met at least one of the following criteria: (1) having been admitted to the long-term care hospital or nursing home; (2) discharge from hospital in the preceding 90 days; (3) elder or physically disability people who need care (ECOG PS score≥3); (4) outpatients who receive infusion therapy (including dialysis, antibiotics, anticancer agent, and immunosuppressant drug). Complications were defined as described previously [9-13]. And then, patients were defined as NHCAP except HCAP when they met the criteria for NHCAP but did not meet the criteria for HCAP. The ECOG PS score ranges from 0 to 5, according to the following classification: 0 (asymptomatic); 1 (symptomatic but completely ambulatory); 2 (symptomatic, <50% of day time spent in bed); 3 (symptomatic, >50% day time spent in bed, but not bed bound); 4 (bed bound); and 5 (death) [8]. In-hospital mortality, hospital stay, and initial treatment failure were also evaluated.

**Microbiological evaluation**

Specimens obtained within 24 hours of admission were eligible for etiologic evaluation, and included sputum, tracheal aspirate, blood, and others. These samples were cultured semi-quantitatively in sheep blood agar, chocolate agar, and BTB lactate agar. With the exception of normal flora, positive bacterial culture results for respiratory

tracts 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*. *Legionella pneumophila* serogroup 1 antigen was detected in urine samples by immunochromatography. The antibiotic sensitivity of bacteria was determined using a microdilution panel (Micro Scan®; Siemens Healthcare Diagnostics Inc.; Tokyo, Japan). *Pseudomonas aeruginosa*, *Acinetobacter* species, and MRSA were considered as MDR pathogens according to the 2005 ATS/IDSA guidelines [1].

**Pneumonia severity**

Pneumonia severity was assessed via the pneumonia severity index (PSI), which was calculated using the following variables: age, gender, complications, and vital sign abnormalities, together with several laboratory, blood gas, and radiographic parameters [14, 15]. Chest X-ray findings were reviewed and assessed blindly by three physicians.

The severity of the pneumonia was also evaluated using the CURB-65 score. The CURB-65 score is a six-point score, with one point added for each of the following criteria: confusion of new onset; urea >7 mmol/l or blood urea nitrogen >19 mg/dL; respiratory rate ≥30 breaths per minute; systolic blood pressure < 90 mmHg or diastolic blood pressure ≤60 mmHg; and age ≥65 years [16].

**Classification of antibiotic**

According to the 2005 ATS/IDSA guidelines [1], HCAP patients should be treated for MDR-pathogens using combination antibiotic therapy, such as antipseudomonal cephalosporin, antipseudomonal carbapenem, β-Lactams/β-Lactamase inhibitor plus antipseudomonal fluoroquinolone, or aminoglycoside. In this study, β-Lactams were classified into antipseudomonal β-Lactams or non-antipseudomonal β-Lactams based on their antibacterial spectrum.

**Parameters of clinical response**

Clinical response was determined by assessing signs and symptoms of respiratory infections, as well as by comparing the baseline versus end of treatment chest X-rays. The clinical response was rated either as a cure if signs and symptoms related to pulmonary infection had disappeared, or as a failure if lessening of symptoms related to pulmonary infection was rated as insufficient or if additional treatment was necessary.

**Statistical analysis**

A statistical software package (StatMate Ⅳ for Windows®; ATMS Co., Ltd., Tokyo, Japan) was used for all statistical comparisons. All comparisons were unpaired, and all tests of significance were two tailed. The α level for denoting statistical significance was set at $<0.05$. Continuous variables were compared using the Student *t*

test when variables were normally distributed and the Mann-Whitney U test when variables were non-normally distributed. The chi-square or Fisher's exact test were used to compare categorical variables. A logistic regression analysis was used to assess the relationship between in-hospital mortality and possible risk factors. The contribution of each potential risk factor was denoted by an odds ratio (OR) and associated 95% confidence interval (CI).

## Results

### Patient characteristics

During the study period, a total of 108 patients with NHCAP were evaluated, comprising 77 patients with HCAP and 31 patients with NHCAP except HCAP. Of the HCAP patients, 55(67.5%) had been hospitalized for 2 or more days in the preceding 90 days and 29 (37.7%) had resided in a nursing home or an extended care facility. Five patients (6.5%) were receiving home infusion therapy (including antibiotics), one (1.3%) received chronic dialysis within 30 days, and another (1.3%) was receiving home wound care. No patients had a family member with the MDR pathogen. The criteria for inclusion in NHCAP are shown in Table 1. 27 (87.1%) of NHCAP except HCAP patients were over 3 in ECOG PS score.

The characteristics of HCAP and NHCAP except HCAP patients are presented in Table 2. NHCAP except HCAP patients were significantly older than HCAP patients (83.7 ± 5.6 versus 77.6 ± 12.7; $P$=0.011). In complications, chronic lung disease was significantly more common among NHCAP except HCAP patients versus HCAP patients. There were no significant differences in ECOG PS score and the rate of aspiration pneumonia and tube feeding between two groups. However, the rate of patients, who were used antibiotics within 90 days, was significantly lower in NHCAP

except HCAP patients compared with HCAP patients. Mechanical ventilation was not used in all patients.

**Pneumonia severity**

The severity of HCAP and NHCAP except HCAP were assessed by means of the PSI criteria and CURB-65 (Table 3). NHCAP except HCAP patients were more frequently classified into high-risk CURB-65 classes compared with HCAP patients (29.0% versus 14.3%; *P=0.067*). However, there were no significant differences between two groups.

**Pathogen distribution**

Details of the bacteria and other organisms identified in HCAP and NHCAP except HCAP groups are shown in Table 4. Bacteria were identified in 28 patients (36.4%) with HCAP and in 9 (29.0%) with NHCAP except HCAP. NHCAP except HCAP patients were significantly more likely to be infected with *Enterobacter cloacae* than were HCAP patients (6.5% versus 0.0%; *P*=0.024). There were no significant differences in frequency of MDR-pathogens between two groups

**Antibiotic treatment and clinical outcomes**

Details of initial antibiotic therapy of HCAP and NHCAP except HCAP patients are listed in Table 5. Initial antibiotics were prescribed according to the

physician's judgment. Most commonly, HCAP and NHCAP except HCAP patients received antibiotic monotherapy (96.1% of HCAP and 90.3% of NHCAP except HCAP patients). Among the antibiotics, antipseudomonal β-Lactams were most used in both groups. In the response rate of initial antibiotic therapy, there were no significant differences between two groups (Table 6).

Although the in-hospital mortality of HCAP and NHCAP except HCAP patients was 9.1% and 19.4%, respectively, this difference did not reach statistical significance ($P>0.05$).

**Discussion**

Our results revealed there are almost no differences in background of patients, disease severity, and initial antibiotic regimens between HCAP and NHCAP except HCAP patients. It suggested that, in the criteria of HCAP, some Japanese patients, who were consistent with the concept of HCAP, were classified into CAP.

In Japan, there were approximately 2,800,000 people who received in-home care [17]. And then, the number was greater than the number of people who received care at facility ( approximately 820,000). In this study, 87.1% of patients with NHCAP except HCAP were over 3 in ECOG PS score and the mean age of patients with NHCAP except HCAP was significantly higher than that of HCAP patients. It indicates that there are many elderly people who received concentrated in-home care in Japan. If the elderly people developed pneumonia at home, we would classify them to HCAP on the basis of the concept of HCAP.

Additionally, in this report, NHCAP except HCAP patients were similar to HCAP patients in the following respects. Firstly, previous study [5] showed that aspiration pneumonia was observed more frequently in HCAP patients compared with CAP patients (20.6% vs 3.0%), and in this study, aspiration pneumonia was observed in over 40% of HCAP patients and NHCAP except HCAP patients. Secondly, most HCAP

patients were at risk for infection with MDR pathogens in the ATS/IDSA guidelines, and in this study, although the rate of use of antibiotics within 90 days was significantly lower in NHCAP except HCAP patients compared with HCAP patients, there was no significantly difference in the rate of MDR-pathogens identified between two groups. Thirdly, in the response rate of initial antibiotic therapy, the outcomes of the use of antipseudomonal β-Lactams for NHCAP except HCAP patients were better than that of non-antipseudomonal β-Lactams. In the ATS/IDSA guidelines, the use of antipseudomonal was recommended for initial antibiotic therapy, thus our results suggested that NHCAP except HCAP patients should be treated as HCAP patients.

However, there were some reviews [4, 5], which gave adverse opinion for the concept of HCAP. They concluded that HCAP is a heterogeneous disease and not all HCAP patients require a broad-spectrum multidrug regimen. Actually, several reports [10, 13, 18-20] from Japan showed various values of frequency of MDR-pathogens and mortality rate of HCAP patients: frequency of MDR-pathogens was 3.3% to 42.9%; and mortality rate was 1.8% to 21.3%. In addition, the recent Japanese study [20] reported that the characteristics of HCAP patients are different between those admitted to large hospitals or small hospitals. Although these study suggested the heterogeneity of HCAP, there might be many patients in Japan, as this study showed, who has been classified

incorrectly to CAP. Hence, in future Japanese studies, we must investigate HCAP according to the criteria of NHCAP, and should discuss whether there is really need for the concept of HCAP. In addition, we must investigate pathogens in detail because pathogens were not identified in many patients and anaerobic bacteria could not be cultured in this study.

In summary, this study revealed the need to change the definition of HCAP according to medical environment in Japan, and the definition of NHCAP seemed to be able to extract bedridden elderly people at home who were consistent with the concept of HCAP. However, because there is a discussion about the need for the concept of HCAP, we should investigate HCAP according to the criteria of NHCAP in future studies.

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Table 1. Criteria of 77 patients with HCAP and 31 patients with NHCAP except HCAP

| Criterion | No. (%) of patients | | | |
|---|---|---|---|---|
| | HCAP (n=77) | | NHCAP except HCAP (n=31) | |
| Having been admitted to the long-term care hospital or nursing home | 29 | (37.7) | 0 | (0.0) |
| Discharge from hospital in the preceding 90 days | 52 | (67.5) | 0 | (0.0) |
| ECOG PS score ≥3 | 41 | (53.2) | 27 | (87.1) |
| outpatients who receive infusion therapy | 0 | (0.0) | 6 | (19.4) |

Table 2. Characteristics of HCAP and NHCAP except HCAP patients

| Characteristics | No. (%) of patients | | | | *P* value |
|---|---|---|---|---|---|
| | HCAP (n=77) | | NHCAP except HCAP (n=31) | | |
| Sex | | | | | |
| Male | 40 | (51.9) | 19 | (61.3) | 0.378 |
| Female | 37 | (48.1) | 12 | (38.7) | |
| Age, years | 77.6 | ± 12.7 | 83.7 | ± 5.6 | 0.011 |
| Age ≥ 65[a] | 69 | (89.6) | 31 | (100) | 0.145 |
| Complications | 73 | (94.8) | 27 | (87.1) | 0.166 |
| Neoplastic disease | 19 | (24.7) | 13 | (41.9) | 0.076 |
| Chronic lung disease | 33 | (42.9) | 20 | (64.5) | 0.042 |
| Chronic heart disease | 28 | (36.4) | 8 | (25.8) | 0.408 |
| Chronic renal disesase | 8 | (10.4) | 0 | (0.0) | 0.145 |
| Chronic liver disease | 4 | (5.2) | 0 | (0.0) | 0.196 |
| Central nerve system disorder | 23 | (29.9) | 7 | (22.6) | 0.444 |
| Diabetes mellitus | 24 | (31.2) | 6 | (19.4) | 0.372 |
| Collagen disease | 7 | (9.1) | 0 | (0.0) | 0.192 |
| Two or more complications | 48 | (62.3) | 19 | (61.3) | 0.919 |
| Performance status (PS) | 2.09 | ± 1.37 | 2.10 | ± 1.16 | 0.983 |
| Probable aspiration | 34 | (44.2) | 13 | (41.9) | 0.833 |
| Tube Feeding | 2 | (2.6) | 1 | (3.2) | 0.857 |
| Use of antibiotics within 90 days | 47 | (61.0) | 4 | (12.9) | <0.001 |
| Mechanical ventilation | 0 | (0.0) | 0 | (0.0) | |

[a] Values are presented as means ± standard deviations.

Table 3. Pneumonia severity of HCAP and NHCAP except HCAP patients

| Pneumonia severity | No. (%) of patients | | | | *P* value |
|---|---|---|---|---|---|
| | HCAP (n=77) | | NHCAP excpet HCAP (n=31) | | |
| PSI score[a] | 122.2 | ± 45.3 | 111.8 | ± 41.4 | 0.271 |
| Low (≤90, Class Ⅰ to Ⅲ) | 19 | (24.7) | 11 | (35.5) | 0.257 |
| Intermediate (91 to 130, Class Ⅳ | 28 | (36.4) | 11 | (35.5) | 0.931 |
| High (>130, Class Ⅴ) | 30 | (39.0) | 9 | (29.0) | 0.331 |
| CURB-65 score[a] | 1.69 | ± 1.08 | 1.87 | ± 1.15 | 0.436 |
| Low (0 to 1) | 40 | (51.9) | 17 | (54.8) | 0.785 |
| Intermediate (2) | 26 | (33.8) | 5 | (16.1) | 0.067 |
| High (≥3) | 11 | (14.3) | 9 | (29.0) | 0.074 |

[a] Values are presented as means ± standard deviations.

Table 4. Frequency of bacteria identified in HCAP and NHCAP except HCAP patients

| Bacteria | No. (%) of patients | | | | *P* value |
|---|---|---|---|---|---|
| | HCAP (n=77) | | NHCAP except HCAP (n=31) | | |
| Gram-positive bacteria | 11 | (14.3) | 6 | (19.4) | 0.513 |
| *Streptococcus pneumoniae* | 4 | (5.2) | 2 | (6.5) | 0.796 |
| *Staphylococcus aureus* | 6 | (7.8) | 3 | (9.7) | 0.949 |
| (MSSA)[a] | 4 | (5.2) | 2 | (6.5) | 0.796 |
| (MRSA)[b] | 2 | (2.6) | 1 | (3.2) | 0.857 |
| Other gram-positive bacteria | 1 | (1.3) | 1 | (3.2) | 0.660 |
| Gram-negative bacteria | 28 | (36.4) | 5 | (16.1) | 0.389 |
| *Haemophilus influenzae* | 4 | (5.2) | 0 | (0.0) | 0.196 |
| (BLNAR)[c] | 1 | (1.3) | 0 | (0.0) | 0.524 |
| *Escherichia coli* | 3 | (3.9) | 0 | (0.0) | 0.265 |
| *Pseudomonas aeruginosa* | 1 | (1.3) | 0 | (0.0) | 0.524 |
| *Klebsiella* species | 4 | (5.2) | 1 | (3.2) | 0.660 |
| *Enterobacter cloacae* | 0 | (0.0) | 2 | (6.5) | 0.024 |
| *Serratia marcescens* | 4 | (5.2) | 0 | (0.0) | 0.196 |
| *Moraxella catarrhalis* | 4 | (5.2) | 0 | (0.0) | 0.196 |
| Other gram-negative bacteria | 4 | (5.2) | 2 | (6.5) | 0.796 |
| *Mycoplasma pneumoniae* | 1 | (1.3) | 1 | (3.2) | 0.502 |
| Negative culture or no culture | 49 | (68.6) | 22 | (71.0) | 0.823 |
| MDR-pathogens | 3 | (3.9) | 1 | (3.2) | 0.867 |

[a] MSSA, meticillin-susceptible *Staphylococcus aureus* .

[b] MRSA, meticillin-resistant *Staphylococcus aureus* .

[c] BLNAR, β-lactamase-negative ampicillin-resistant *Haemophilus influenzae.*

Table 5. Antibiotic therapy and clinical outcomes of HCAP and NHCAP except HCAP pat

| Therapy and outcomes | No. (%) of patients | | | | *P* value |
|---|---|---|---|---|---|
| | HCAP (n=77) | | NHCAP except HCAP (n=31) | | |
| Initial antibiotic treatment | | | | | |
| Monotherapy | 74 | (96.1) | 28 | (90.3) | 0.235 |
| Antipseudomonal β-Lactams | 41 | (53.2) | 19 | (61.3) | 0.447 |
| Non-antipseudomonal β-Lactams | 31 | (40.3) | 7 | (22.6) | 0.082 |
| Quinolones | 2 | (2.6) | 1 | (3.2) | 0.857 |
| Other | 0 | (0.0) | 1 | (3.2) | 0.113 |
| Combination therapy | 3 | (3.9) | 3 | (9.7) | 0.235 |
| β-Lactams + macrolides | 1 | (1.3) | 0 | (0.0) | 0.524 |
| β-Lactams + lincomycins | 0 | (0.0) | 2 | (6.5) | 0.024 |
| β-Lactams + quinolones | 1 | (1.3) | 1 | (3.2) | 0.502 |
| β-Lactams + aminoglycoside | 1 | (1.3) | 0 | (0.0) | 0.524 |
| Initial treatment failure | 22 | (28.6) | 11 | (35.5) | 0.481 |
| In-hospital mortality | 7 | (9.1) | 6 | (19.4) | 0.248 |
| Hospital stay (days)[a] | 19.1 | ± 17.6 | 18.0 | ± 12.1 | 0.783 |

[a] Values are presented as means ± standard deviations.

Table 6. Response rates of initial antibiotic therapy

| Initial antibiotic treatment | Response rate | | | | *P* value |
|---|---|---|---|---|---|
| | HCAP (n=77) | | NHCAP except HCAP (n=31) | | |
| Monotherapy | 71.6% | (53/74) | 71.4% | (20/28) | 0.985 |
| Antipseudomonal β-Lactams | 73.1% | (30/41) | 78.9% | (15/19) | 0.873 |
| Non-antipseudomonal β-Lactams | 67.7% | (21/31) | 57.1% | (4/7) | 0.593 |
| Quinolones | 100% | (2/2) | 0.0% | (0/1) | 0.333 |
| Other | | | 100% | (1/1) | |
| Combination therapy | 66.7% | (2/3) | 0.0% | (0/3) | 0.200 |
| β-Lactams + macrolides | 100% | (1/1) | | | |
| β-Lactams + lincomycins | | | 0.0% | (0/2) | |
| β-Lactams + quinolones | 0.0% | (0/1) | 0.0% | (0/1) | |
| β-Lactams + aminoglycoside | 100% | (1/1) | | | |