MAJOR ARTICLE

Epidemiology, Antibiotic Therapy, and Clinical Outcomes in Health Care–Associated Pneumonia: A UK Cohort Study

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Background. The recently introduced concept of health care–associated pneumonia (HCAP), referring to patients with frequent healthcare contacts and at higher risk of contracting resistant pathogens, is controversial.

Methods. This prospective observational study recorded the clinical features, microbiology, and outcomes in a UK cohort of hospitalized patients with pneumonia. The primary outcome was 30-day mortality. Logistic regression was used to adjust for confounders when determining the impact of HCAP on clinical outcomes.

Results. A total of 20.5% of patients met the HCAP criteria. HCAP patients were older than patients with community-acquired pneumonia (CAP) (median 76 y, IQR 65–83 vs 65 y, IQR 48–77; $P < .0001$) and more frequently had major comorbidities (62.1% vs 45.2%; $P < .0001$). Patients with HCAP had higher initial severity compared to CAP patients (Pneumonia Severity Index, mean 3.7 [SD 1.1] vs mean 3.1 [SD 1.3]; $P < .0001$) but also worse functional status using the Eastern Cooperative Oncology Group scale (mean 2.4 [SD 1.44] vs mean 1.4 [SD 1.13]; $P < .0001$) and more frequently had treatment restrictions such as do not resuscitate orders (59.9% vs 29.8%; $P < .0001$). Consequently mortality was increased (odds ratio [OR] 2.15 [1.44–3.22]; $P = .002$) in HCAP patients on univariate analysis. Multivariate analysis suggested this relationship was primarily due to confounders rather than a higher frequency of treatment failure due to resistant organisms (adjusted OR .97 [.61–1.55]; $P = .9$). The frequencies of *Pseudomonas aeruginosa,* methicillin-resistant *Staphylococcus aureus,* and Gram-negative Enterobacteriaceae were low in both cohorts.

Conclusions. HCAP is common in the United Kingdom and is associated with a high mortality. This increased mortality was primarily related to underlying patient-related factors rather than the presence of antibiotic-resistant pathogens. This study did not establish a clear indication to change prescribing practices in a UK cohort.

Pneumonia has traditionally been classified as either community or hospital acquired [1, 2]. This distinction is critical to further management because community-acquired pneumonia (CAP) is typically caused by organisms such as *Streptococcus pneumoniae* that are sensitive to most first-line antibiotics [1], while hospital-acquired pneumonia (HAP) is typically caused by drug-resistant pathogens such as *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and Gram-negative Enterobacteriaceae [2]. Patients with HAP therefore require broad-spectrum initial therapy [2]. The combination of resistant, difficult-to-treat organisms, along with the comorbid illnesses that accompany HAP, lead to a worse prognosis [2].

The average age of the population in Western countries is increasing and consequently recent years have seen an increase in the number of elderly patients hospitalized with pneumonia [3]. These demographic changes have increased the number of predominantly elderly patients who regularly enter healthcare facilities [4]. In recognizing this, the 2005 Infectious Diseases Society of America/American Thoracic Society (IDSA/

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ATS) guidelines created a third classification of pneumonia, health care–associated pneumonia (HCAP) [2]. The groups included in this definition are shown in Table 1. A large retrospective study published at the same time as the guidelines suggested that HCAP patients had a similar microbiology and outcome to those with HAP [5]. Consequently it was recommended that patients with HCAP should receive broad-spectrum antimicrobial therapy directed against drug-resistant, health care–acquired pathogens [2].

This concept has been controversial. Some studies, predominantly from the United States, have supported an increased frequency of drug-resistant pathogens in HCAP and a higher mortality [5–8]. In contrast, 2 studies in Southern Europe have shown a lower frequency of drug-resistant pathogens and have not fully confirmed an association between narrow-spectrum therapy and poor outcome [9–11]. A study of nursing home–acquired pneumonia (one of the largest HCAP groups) from Spain also found a mortality rate and microbiological spectrum more similar to CAP than to HAP [12]. This has led some authors to question the value of HCAP as a concept outside the United States [11–13].

The aim of this study was to describe the epidemiology, clinical features, antibiotic treatment, and outcomes of HCAP patients to investigate the clinical value of this concept in a United Kingdom (UK) pneumonia cohort.

METHODS

This was a prospective observational study of patients hospitalized with pneumonia in Edinburgh, United Kingdom. Data collection commenced in 2005. The present analysis was conducted from January 2005 to May 2009. Analysis was limited to May 2009 as the first wave of the UK H1N1 influenza pandemic subsequently changed the epidemiology of CAP significantly in the study hospitals [14]. The study was approved by the Lothian Research Ethics Committee.

Definition of Community-Acquired and Health care–Associated Pneumonia

Patients were included in the study if they presented with a new radiographic infiltrate and had 3 or more of the following symptoms or signs: cough, sputum production, hemoptysis, breathlessness, fever, pleuritic chest pain, or signs consistent with pneumonia on physical examination. Patients with hospital-acquired pneumonia, active thoracic malignancy, or immunosuppression (defined as use of oral corticosteroids or other immunosuppressive drugs within the previous 28 days) and patients in whom active treatment was not considered appropriate (palliative care) were excluded from the study [15, 16].

Health care–associated pneumonia was defined according to the 2005 IDSA/ATS criteria (Table 1). Patients meeting any of these criteria were classified as having HCAP [2]. Two independent investigators (JDC and JKT) validated the assignment of patients to either HCAP or CAP categories in a blinded fashion with any disagreement resolved by a third independent adjudicator (ATH).

Table 1. Criteria for HCAP Patients According to the 2005 IDSA/ATS Guidelines

Criteria for HCAP (IDSA/ATS 2005 guidelines) [2]. Any one of the following:
Hospitalization for 2 days or more in the preceding 90 days
Resident of a nursing home or extended-care facility
Home infusion therapy (including antibiotics) [a]
Chronic dialysis within 30 days
Home wound care
Family member with multidrug-resistant pathogen

NOTE. HCAP, health care–associated pneumonia; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society.

[a] Also includes patients with long-term indwelling devices such as catheters.

Patient data were linked to an administrative database that records all hospital admissions within the region to ensure all hospitalizations within the preceding 3 months were accurately recorded.

Clinical Assessment and Severity Indices

All patients attended an emergency department at one of the study hospitals. Initial observations and laboratory tests were obtained within 4 hours in accordance with national guidelines. Recommended initial microbiology investigations were as follows: blood and sputum culture and *Legionella* urinary antigen and throat swab (polymerase chain reaction for respiratory viruses and atypical organisms). Patients were risk assessed on admission using the Pneumonia Severity Index (PSI) and CURB-65 scores [17]. In addition to routinely collected clinical variables, we recorded patient treatment restrictions (advanced directives and "do not resuscitate" or "not for ICU" orders) and risk factors for aspiration pneumonia, in order to adjust for these in analysis, as these have been reported as limitations of previous studies of HCAP [11]. There are no recognized guidelines to define risk factors for aspiration and therefore the authors defined patients at risk of aspiration as those patients with impaired swallowing due to neurological disease (multiple sclerosis, cerebrovascular disease); mechanical obstruction or esophageal dysfunction (stricture, carcinoma, or other cause of dysphagia); impaired consciousness (including drug overdose, seizure, acute alcohol consumption, or collapse); or a history of vomiting or witnessed aspiration. Functional status was assessed using the system developed by the Eastern Cooperative Oncology Group [18].

Initial antibiotic therapy during the study period for CAP recommended combination β-lactam plus macrolide for all

hospitalized patients with CAP. For moderately or severely ill patients, ceftriaxone 2 g/24 h or amoxicillin/clavulanic acid 1.2 g/8 h plus clarithromycin 500 mg/12 h was recommended. Amoxicillin 500 mg/8 h plus clarithromycin 500 mg/12 h was recommended for nonseverely ill patients. Fluoroquinolones were not part of the local guideline for CAP in the study hospitals and were only recommended for patients with *P. aeruginosa* or patients intolerant of macrolides. Prescribing decisions were at the discretion of the attending physician.

For patients with HAP, therapy was recommended to cover *P. aeruginosa* and Gram-negative Enterobacteriaceae (recommended agents were piperacillin/tazobactam, ceftazidime, and gentamicin) and MRSA (recommended agents were vancomycin and linezolid). No guidelines exist for the treatment of HCAP in the United Kingdom and the concept is not widely recognized.

Outcomes

Patients were followed up for 30 days from date of admission. We recorded 30-day mortality and need for mechanical ventilation and/or vasopressor support. Survival status was confirmed in 100% of the study population.

We hypothesized that, if previous reports of worse clinical outcomes and a greater frequency of antibiotic-resistant pathogens in the HCAP group held true, HCAP would be associated with worse 30-day mortality independent of confounders.

Statistical Analysis

Data were analyzed using SPSS software version13.0 (SPSS). The χ-square test was used to compare categorical data, with Fisher exact test used where any cell contained less than 10. The Mann-Whitney *U* test was used for comparison of 2 groups of continuous data. To adjust for potential confounders, we performed 2 multivariate logistic regression analyses. The first adjusted for confounders generally available in CAP databases, including comorbidities, initial severity (PSI score), and antibiotic treatment (prior antibiotic therapy, inadequate initial antibiotic therapy, and time to first antibiotic dose) with HCAP as an independent variable. As the PSI is heavily weighted by age, it is convention not to also adjust for age in epidemiological studies [19, 20]. A second analysis was performed entering HCAP status as an independent variable and adjusting for the above factors in addition to risk factors for aspiration and functional status. This analysis was then repeated after excluding patients with treatment restrictions to account for an imbalance in treatment restrictions between the HCAP and CAP cohorts.

In each logistic regression analysis, model adequacy was assessed by the Hosner-Lemeshow goodness-of-fit test. For all analyses, a P value $< .05$ was considered statistically significant.

RESULTS

The study included 1348 patients presenting to the emergency department with pneumonia. For the overall cohort, the 30-day mortality rate was 9.0%, and 7.5% of the study population received mechanical ventilation or vasopressor support (MV/VS). Median length of stay was 5 days (IQR 2–12).

Health care–Associated Pneumonia

Using the 2005 IDSA/ATS guideline definition, 277 patients were classified as HCAP (20.5% of the overall cohort) with the remaining patients categorized as CAP. The underlying reasons for HCAP in this cohort are shown in Table 2. The most frequent reasons were hospitalization within the preceding 3 months and residence in a long-term-care facility, accounting for 73.3% of cases.

In the demographic comparison, patients with HCAP were older; had a higher frequency of congestive cardiac failure, cerebrovascular disease, and COPD; and had worse functional status than patients with CAP. In addition, patients with HCAP had a significantly higher frequency of risk factors for aspiration pneumonia (Table 3).

Microbiology and Antibiotic Therapy

A positive microbiological diagnosis was made in 32.1% of patients with HCAP compared with 30.0% of patients with CAP. The frequency of the organisms isolated in each group are shown in Table 4. *S. pneumoniae* was the most frequent pathogen in both groups, and both CAP and HCAP groups demonstrated patterns more similar to those reported in the literature for CAP rather than for HAP. Gram-negative Enterobacteriaceae (2.9%), *P. aeruginosa* (0.7%), and MRSA (1.0%) were all infrequent in the overall cohort. These organisms were all more frequent in HCAP patients, although these differences were not statistically significant due to the low number of isolates generally.

Examining different risk factors for HCAP, the causative organisms were identified in 32.7% of nursing home residents. Fifty percent of these isolates were *S. pneumoniae*. Gram-negative Enterobacteriaceae (2.0%) and *P. aeruginosa* (1.0%) were rarely identified. In patients hospitalized in the previous 3 months, etiology was identified in 33.3% of cases. *S. pneumoniae* was the most frequent isolate (55.6% of positive cases). Gram-negative Enterobacteriaceae accounted for 8.3% of cases, with MRSA and *P. aeruginosa* each accounting for only 1.9% of cases in this group.

The vast majority of patients received initial antibiotic therapy in line with local CAP guidelines. In the CAP cohort, 96.0% received treatment in line with CAP guidelines (without empirical coverage of *P. aeruginosa* or MRSA). The remaining patients received at least 1 agent recommended for HAP and active

Table 2. Numbers of HCAP Patients in Each of the IDSA/ATS 2005 Risk Categories for HCAP [a]

Health care–Associated pneumonia risk factors	
Hospitalized within 3 months	105 (37.9%)
Residence in a long-term–care facility	98 (35.4%)
Home infusion therapy	26 (9.4%)
Home wound care	32 (11.6%)
Outpatient hemodialysis	7 (2.5%)
Known colonization with resistant pathogens	18 (6.5%)

NOTE. HCAP, health care–associated pneumonia; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society.

[a] Numbers and percentages add up to >277 and 100% as some patients have more than 1 risk factor.

against *P. aeruginosa* or MRSA. In the HCAP cohort, 92.8% of patients received treatment consistent with CAP guidelines as above, with only 7.2% receiving agents recommended for HAP and active against *P. aeruginosa* and/or MRSA.

Severity of Pneumonia and Outcomes

Patients with HCAP had a higher initial severity as measured by the CURB-65 scale (HCAP: CURB-65, mean 2.4 [SD 1.3]; CAP: CURB-65, mean 1.9 [SD 1.3]; $P < .0001$) and PSI score (HCAP: mean 3.7 [SD 1.1]; CAP: mean 3.1 [SD 1.3]; $P < .0001$). This relationship was similar for different risk factors for HCAP. Nursing home residents (CURB-65, mean 2.4 [SD 1.2]; PSI, mean 3.8 [SD 1.0]), patients hospitalized in the previous 3 months (CURB-65, mean 2.1 [SD 1.3]; PSI, mean 3.6 [SD 1.1]), and patients with other risk factors (CURB-65, mean 2.3 [SD 1.4]; PSI, mean 3.7 [SD 1.2]).

In univariate analysis, HCAP was associated with an increased 30-day mortality of 14.8%, compared with 7.5% in CAP patients ($P = .002$). HCAP, however, was not associated with an increased rate of mechanical ventilation or vasopressor support (HCAP: 5.8%; CAP: 7.9%; $P = .3$).

The univariate odds ratio (OR) for HCAP and 30-day mortality was 2.15 (1.44–3.22; $P = .002$), but this reduced to a nonsignificant association (OR 1.29 [0.83–2.01]; $P = .3$) after adjustment for baseline PSI, comorbidities, and antibiotic therapy. In the fully adjusted model, taking account of risk factors for aspiration and premorbid functional status, this trend disappeared entirely (OR 0.97 [0.61–1.55]; $P = .9$). The Hosner-Lemeshow goodness-of-fit test was $P > .05$ for both models.

Similarly, there was no relationship between HCAP and requirement for MV/VS. In univariate analysis, HCAP was "protective" against MV/VS. After adjustment for comorbidities and PSI class, this association was nonsignificant (adjusted odds ratio [AOR] 0.78 [0.45–1.37]; $P = .4$) and after adjustment for functional status and risk factors for aspiration the AOR was 0.97 (0.55–1.73; $P = .9$). The Hosner-Lemeshow test indicated adequate fit for all models ($P > .05$).

In a sensitivity analysis, among patients only treated according to CAP guidelines, HCAP was not associated with an increase in 30-day mortality (AOR 0.93 [0.57–1.50]; $P = .8$).

As 73.3% of HCAP patients were either resident in a long-term–care facility or hospitalized within the previous 3 months, a sensitivity analysis was performed including only these groups. In this model, neither residence in a long-term–care facility (AOR 0.94 [0.49–1.81]; $P = .9$) nor hospitalization within 3 months (AOR 0.93 [0.44–1.95]; $P = .8$) was independently associated with 30-day mortality.

Table 3. Demographic Comparison of Patients With CAP and Those With HCAP

	CAP patients	HCAP patients	*P* value
N	1071	277	
Demographics			
Age, median (IQR)	65 (48–77)	76 (65–83)	<.0001
Gender, % male	48.9%	53.8%	.2
Comorbidities			
Congestive cardiac failure	15.8%	29.6%	<.0001
Liver disease	4.9%	4.3%	.8
Renal failure	6.3%	8.3%	.3
Cerebrovascular disease	10.1%	18.8%	.0001
COPD	18.3%	30.0%	<.0001
Diabetes	9.3%	13.4%	.06
Risk factors for aspiration	11.6%	22.4%	<.0001
Functional status, mean (SD)	1.4 (1.13)	2.4 (1.44)	<.0001

NOTE. CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; HCAP, health care–associated pneumonia; IQR, interquartile range.

Patients With Treatment Restrictions

59.9% of patients with HCAP had treatment restrictions compared with 29.8% of patients with CAP ($P < .0001$). Repeating the multivariate analysis in patients without treatment restrictions, HCAP was not associated with 30-day mortality (AOR 0.57 [0.20–1.64]; $P = .3$) or requirement for MV/VS (AOR 0.72 [0.30–1.70]; $P = .4$).

Patients with treatment restrictions were generally elderly (median age 81 y; IQR 71–85) and had poor functional status (mean 2.9 [SD 1.2]). Among nursing home residents, treatment

Table 4. Comparison of Microbiology Results in the CAP and HCAP Groups

Organism	HCAP patients	CAP patients	*P* value
Typical and atypical CAP organisms			
Streptococcus pneumoniae	49.4%	59.8%	0.1
Haemophilus influenzae	14.6%	8.4%	0.1
Staphylococcus aureus[a]	10.1%	9.3%	0.9
Legionella pneumophila	3.4%	4.7%	0.8
Mycoplasma pneumoniae	1.1%	7.2%	0.06
Respiratory viruses	5.6%	5.6%	0.9
Chlamydophila pneumoniae	2.2%	0%	0.07
Other[b]	2.2%	2.8%	0.5
Organisms associated with HCAP			
Gram-negative Enterobacteriaceae	6.7%	1.9%	0.2
Pseudomonas aeruginosa	2.2%	0.3%	0.2
MRSA	2.2%	0.6%	0.4
Stenotrophomonas maltophilia	1.1%	0%	0.5

NOTE. CAP, community-acquired pneumonia; HCAP, health care–associated pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*. Numbers may add to >100% as a small number of patients isolated more than 1 organism.

[a] These *S. aureus* isolates were all methicillin sensitive; methicillin-resistant isolates are considered separately.

[b] Other pathogens were rare but included *Streptococci* other than *S. pneumoniae* and *Moraxella catarrhalis*.

restrictions were present in 73.5% and among those hospitalized in the previous 3 months, 41.0% had documented treatment restrictions.

Risk Factors for High-Risk Organisms

In a logistic regression analysis, the factors most strongly associated with isolation of resistant organisms associated with HCAP (see list above in table 4) were risk factors for aspiration (AOR 3.67; 95% CI = 1.32–10.2; $P = .01$), HCAP (AOR 4.76; 95% CI = 1.82–12.4; $P = .002$), chronic lung disease (AOR 4.0; 95% CI = 1.47–10.9; $P = .007$), and intensive care unit admission (AOR 6.91; 95% CI = 2.06–23.2; $P = .002$).

DISCUSSION

The 2005 IDSA/ATS guidelines established a new concept of health care–associated pneumonia, describing a population of patients with frequent healthcare contacts and therefore at higher risk of contracting resistant organisms [2, 4–13]. Data published shortly after the guidelines found that patients with HCAP had a high mortality rate and grew a spectrum of organisms more similar to HAP than to CAP [5]. These findings have been confirmed in a number of studies in the United States demonstrating higher mortality rates in patients with HCAP and a higher frequency of Gram-negative organisms, *S. aureus, P. aeruginosa,* and others not typically associated with CAP [5–8].

The concept has become controversial, however, as studies from Europe have suggested a microbiology spectrum more similar to CAP and have failed to fully validate this concept outside the United States [9–12]. Studies from Europe have indicated a low frequency of *P. aeruginosa* and Gram-negative Enterobacteriaceae [9–12]. Some authors are now questioning whether the definition of HCAP should be refined or entirely abandoned [4, 11, 13]. In the UK, doubts over the concept of HCAP are reflected in the 2009 CAP guidelines, where HCAP is not recognized as a distinct concept [1].

The aim of this study was to investigate the epidemiology, clinical features, and outcomes of a large cohort of UK patients with HCAP.

Among the major findings, HCAP was common, affecting 20.5% of patients previously classified as CAP. The frequency of HCAP in this study is similar to that reported by Kollef et al (21.9%) in the United States [5] and by researchers in Spain (17.3%) [9] and Italy (24.9%) [10] but lower than others using a broader HCAP definition (67.4% in the study by Micek et al) [6].

In this study, compared with patients with CAP, HCAP patients had a higher mortality. Although this has been demonstrated previously, the underlying reasons for this increased mortality have not previously been investigated in detail. This study found that patients with HCAP had a higher age and frequency of comorbidities. Patients with HCAP were more likely to have risk factors for aspiration and were more likely to have treatment restrictions. They were therefore not more likely to have received mechanical ventilation or vasopressor support. After adjustment for patient factors, HCAP was not independently associated with 30-day mortality.

The principal practical implication of the concept of HCAP is the recommendation that these patients should be treated with broad-spectrum antibiotic therapy, similar to HAP patients [2]. The extended use of broad-spectrum agents to more than 20% of patients currently treated as CAP must be rigorously justified,

however, as elderly patients with comorbidities are most at risk of HCAP but are also at highest risk of antibiotic-related complications [21].

This study did not establish a clear justification for this change in our UK cohort. The incidence of resistant organisms was low in both HCAP and CAP groups, and the sensitivity of the HCAP concept to detect high-risk organisms was only 55%. Most important, broadening antibiotic therapy is only justified if these patients have an excess mortality that may be reduced by increasing antibiotic coverage [13]. Our study did not clearly demonstrate a higher frequency of 30-day mortality or complications once important confounders were taken into account. Our findings suggest that the increased mortality observed in HCAP patients is primarily due to the characteristics of these patients, rather than inadequate empirical therapy for resistant pathogens.

Our study was specifically designed to address some of the limitations of previous studies [11]. In particular, we recorded data on risk factors for aspiration, premorbid functional status, and treatment limitations, all of which have been shown to be major confounders [11].

The microbiology data in this study were limited but found HCAP patients to be more similar to CAP than HAP in terms of the organisms isolated. *S. pneumoniae* was the most frequent organism in both groups and the majority of isolates from HCAP patients would be sensitive to standard CAP therapy. In this regard, our study confirms previous findings in the United Kingdom by Lim [22], who reported no major differences in the etiology between nursing home patients (now regarded as HCAP) and CAP patients. Of note, very few studies of etiology have been conducted over the past 10 years in the United Kingdom [23].

Where do we go from here? It has been suggested that the concept of HCAP should be refined to improve detection of resistant pathogens [11, 13]. Our study was limited due to the low number of such pathogens identified. Allowing for this, however, we did identify additional risk factors for resistant pathogens, namely, chronic lung disease, ICU admission, and risk factors for aspiration [1]. None of these findings are novel, as each is well recognized to be associated with Gram-negative Enterobacteriaceae, MRSA, or *P. aeruginosa* [24–27]. These risk factors, however, are not currently included in the concept of HCAP.

Interestingly, a large study from Germany has also recently demonstrated a very low incidence of *P. aeruginosa* and Gram-negative Enterobacteriaceae in patients with CAP (patients with HCAP were NOT excluded) [28]. The 1.3% incidence of these organisms in the CAPNETZ study and the low incidence reported here compare with the 11.6% frequency of these organisms reported in a study from the United States [6] and around 10% in an influential study from Spain [29]. While there are clear methodological differences between these studies, our data suggest that, at least in Northern Europe, resistant organisms in HCAP may be less of a problem [30].

In conclusion, HCAP is common in the United Kingdom and associated with a high 30-day mortality. This increased mortality was primarily related to underlying patient factors rather than the presence of antibiotic-resistant pathogens. This study did not establish a clear indication to change prescribing practices in a UK cohort.

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