Infectious Diseases

ISSN: 2374-4235 (Print) 2374-4243 (Online) Journal homepage: informahealthcare.com/journals/infd20

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To cite this article: Agnar Bjarnason, Hilmir Asgeirsson, Olafur Baldursson, Karl G. Kristinsson & Magnus Gottfredsson (2015) Mortality in healthcare-associated pneumonia in a low resistance setting: a prospective observational study, Infectious Diseases, 47:3, 130-136, DOI: 10.3109/00365548.2014.980842

To link to this article: https://doi.org/10.3109/00365548.2014.980842

Infectious Diseases, 2015; 47: 130–136

informa
healthcare

ORIGINAL ARTICLE

Mortality in healthcare-associated pneumonia in a low resistance setting: a prospective observational study

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Abstract

Background: The classification of pneumonia as community-acquired pneumonia (CAP) or healthcare-associated pneumonia (HCAP) has implications for selection of initial antimicrobial therapy. HCAP has been associated with an increased prevalence of multidrug-resistant (MDR) pathogens and with high mortality leading to recommendations for broad empiric therapy. *Methods:* We performed a prospective, population-based study on consecutive adults (≥18 years) admitted for pneumonia over 1 calendar year. Patients were classified by pneumonia type and severity. Microbial etiologic testing was performed on all patients. Treatment, length of stay, and mortality rates were compared. *Results:* A total of 373 admissions were included, 94% of all eligible patients. They were classified as CAP ($n = 236$, 63%) or HCAP ($n = 137$, 37%). Chronic underlying disease was more commonly found among patients with HCAP compared with CAP (74% vs 51%, $p < 0.001$). *Mycoplasma pneumoniae* was more common among CAP patients ($p < 0.01$), while gram-negative bacteria were more often found among HCAP patients ($p = 0.02$). No MDR pathogens were detected, and rates of *Staphylococcus aureus* were similar in the two groups. HCAP patients were not more likely to receive ineffective initial antimicrobial therapy. HCAP patients had worse prognostic scores on admission and higher in-house mortality than CAP patients (10% vs 1%, respectively, $p < 0.01$). *Conclusions:* Even in a low resistance setting, patients with HCAP have increased mortality compared with patients with CAP. This is most likely explained by a higher prevalence of co-morbidities. Our data do not support broad-spectrum empiric antibiotic therapy for HCAP.

Keywords: *Healthcare-associated pneumonia, community-acquired pneumonia, antimicrobial resistance, etiology, mortality*

Introduction

Pneumonia is a common disease that frequently requires hospital admission and is a leading cause of mortality worldwide. Based on the setting for diagnosis, the disease is often divided into three major groups: community-acquired pneumonia (CAP), healthcare-associated pneumonia (HCAP), and hospital-acquired pneumonia (HAP) [1]. The HCAP designation is designed to identify patients with risk factors for multidrug-resistant (MDR) pathogens [2].

Patients with HCAP have higher mortality rates than those with CAP, ranging from 10% to 25% of admitted patients [3–8]. Management of HCAP has been addressed in guidelines recommending broad-spectrum antibiotic treatment to ensure effective initial therapy [2]. However, the prevalence of MDR pathogens varies between studies. An important MDR pathogen, methicillin-resistant *Staphylococcus aureus* (MRSA), has been identified as the cause of pneumonia in up to 30% of cases [4,5] and *Pseudomonas* species are the etiologic cause in 10–26% of diagnosed patients with HCAP [5,8,9]. Increased rates of methicillin-susceptible *Staph. aureus* (MSSA), gram-negative pathogens, and penicillin-resistant *Streptococcus pneumoniae* in comparison with patients with CAP have been described [4–6].

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(Received 3 July 2014; accepted 20 October 2014)

ISSN 2374-4235 print/ISSN 2374-4243 online
DOI: 10.3109/00365548.2014.980842

It has been demonstrated that HCAP patients often receive inappropriate initial therapy, which correlates significantly with mortality [4,5,7,8]. Another explanation possibly contributing to worse outcomes is that the HCAP criteria select patients who are frail and less likely to survive their illness irrespective of pathogen, which is supported by the higher age and greater number of co-morbidities in this group [4,6,8–12]. This could be clarified by examining outcomes for HCAP patients in an area with low levels of resistant pathogens, but unfortunately such studies are lacking.

We performed a prospective, population-based study of patients admitted for pneumonia in Iceland, a setting where the prevalence of MDR pathogens is low. The aim of the study was to compare CAP and HCAP with respect to clinical and microbiological characteristics, treatment, and outcomes.

Materials and methods

Setting and study design

This prospective, population-based study was conducted at Landspitali University Hospital, Reykjavík, Iceland. The hospital provides secondary care for two-thirds of the population and intensive care for over 90% [13]. Consecutive adult patients (≥ 18 years) admitted for pneumonia from December 1, 2008 to November 30, 2009 were recruited during their first 24 h of admission. Participants who met inclusion criteria were classified as having either CAP or HCAP and samples were collected for etiologic testing. Data collected for analysis included vital signs and symptoms, and initial and definite antimicrobial therapy received (defined as the drug administered $>50\%$ of the treatment period). Pneumonia severity index (PSI) and CURB-65 were calculated from presenting values and APACHE II scores were calculated using data from the first 24 h of admission [14–16]. Study end points were length of stay (LOS), admission to intensive care units (ICUs), need for mechanical ventilation, and in-house mortality.

Patient selection

Patients were included if they met criteria for new-onset pneumonia (new infiltrate on chest X-ray and at least two of the following: temperature $<36°C$ or $>38.3°C$, diaphoresis (profuse sweating), chills, chest pain, new onset of cough or dyspnea) [17]. Patients presenting within 14 days of discharge after a hospital admission were excluded. All patients or a proxy (close relative) provided written informed consent. The study was approved by the Landspitali University Hospital ethics committee and conducted in accordance with the amended Declaration of Helsinki.

Participants were classified as having HCAP if the they met the following criteria: admission from a long-term nursing facility, hospitalization for ≥ 2 days in an acute care facility within the last 90 days, use of ≥ 5 mg of prednisolone or equivalent during the preceding 30 days, use of other immunosuppressive medications (including: methotrexate, hydroxyurea, adalimumab, infliximab, etanercept, azathioprine, mycophenolate mofetil or cyclosporine), solid organ recipient or undergoing treatment for malignancy [2,5,17]. Otherwise patients were included in the CAP group.

Etiological investigations

Etiology was determined with sputum and blood cultures, urinary antigen testing, and PCR (polymerase chain reaction) analysis as described previously [13]. Susceptibility testing was performed using the Clinical and Laboratory Standards Institute (CLSI) methods and criteria [18].

Statistical analysis

Statistical calculations and regression analysis were performed using IBM SPSS Statistics version 19.0.0 (IBM, Armonk, NY, USA). Continuous data were compared using Student's t test. Categorical data were compared with the chi-squared test or Fisher's exact test when appropriate. Multinomial logistic regression analysis was performed examining age, pneumonia class, and underlying conditions as risk factors for mortality. Two-tailed significance was set at $p \leq 0.05$.

Results

Of 511 patients with suspected pneumonia, 15 (2%) declined and 123 (24%) participants did not meet inclusion criteria. A total of 373 admissions were included, 94% of all admissions for pneumonia during the study period. Over half were classified as CAP ($n = 236$, 63%), with the remaining patients falling into the HCAP group ($n = 137$, 37%). Table I displays the occurrence of risk factors used for classification.

Clinical characteristics and underlying conditions are presented in Table II. Patients with HCAP were older and more often had an underlying disease. Severity scores in this group were higher, predicting worse outcomes.

Table I. Occurrence of classification factors for CAP or HCAP.[a]

Risk factor	CAP ($n = 236$)	HCAP ($n = 137$)
Long-term nursing care	0 (0)	30 (22)
Admission to acute care facility within 14–90 days	0 (0)	61 (45)
Malignancy	8 (3)[b]	18 (13)
Corticosteroid treatment	5 (2)[c]	59 (43)
Hemodialysis	0 (0)	2 (1)

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia.
[a]Data presented as *n* (%). As individual patients can have multiple risk factors, percentages can exceed 100%.
[b]Patients with malignancy but not receiving active treatment.
[c]Corticosteroid on admission at doses equivalent to <5 mg.

Sample acquisition and etiologic diagnosis occurred at the same rate in both groups. Blood cultures were collected from 280 (75%) participants and 194 (52%) provided sputum, with 117 (31%) samples of acceptable quality [19]. As shown in Table III, *Strep. pneumoniae* was the most common pathogen encountered in both groups. *Mycoplasma pneumoniae* and influenza were more commonly identified among CAP patients, while gram-negative pathogens and *Legionella* species were more often found among HCAP patients.

No MDR bacteria (i.e. resistant to three or more antimicrobial classes) were found in our study. Strains of *Acinetobacter* species, *Burkholderia pseudomallei*, and *Pseudomonas aeruginosa* were encountered but were not multiresistant. The Enterobacteriaceae found were susceptible to most antimicrobial agents tested.

Table III. Distribution of diagnosed pathogens between patient groups.[a]

Variables	CAP ($n = 236$)	HCAP ($n = 137$)	*p* value[b]
Diagnosed cases	107 (45)	54 (39)	NS
Cases with two pathogens	10 (4)	6 (4)	NS
Etiologic agents			
Streptococcus pneumoniae	30 (28)	22 (41)	NS
Haemophilus influenzae	15 (14)	5 (9)	NS
Moraxella catarrhalis	5 (5)	3 (6)	NS
Staphylococcus aureus	5 (5)	3 (6)	NS
β-Hemolytic streptococci	4 (4)	2 (4)	NS
Mycoplasma pneumoniae	30 (28)	6 (11)	0.009
Chlamydophila pneumoniae	3 (3)	2 (4)	NS
Legionella species	1 (1)	4 (7)	0.044
Gram-negative bacilli[c]	2 (1)	6 (11)	0.020
Influenza A and B	22 (21)	3 (6)	0.012
Mycobacteria	0 (0)	2 (4)	NS
Pneumocystis jirovecii	0	1 (2)	NS
Parainfluenza 2	0 (0)	1 (2)	NS

CAP, community-acquired pneumonia; HCAP, healthcare-associated pneumonia.
[a]Data expressed as *n* ().
[b]Calculations included only diagnosed cases.
[c]*Acinetobacter* species, *Burkholderia pseudomallei, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Stenotrophomonas maltophilia.*

As shown in Table IV, both patient groups received comparable antimicrobial treatment regimens. However, HCAP patients were more likely to receive a cephalosporin and less likely to receive combination therapy with a β-lactam and a macrolide.

Comparison of culture results and treatment indicated that HCAP patients were not more likely

Table II. Comparison of characteristics and outcomes.[a]

Variable	CAP ($n = 236$)	HCAP ($n = 137$)	*p* value
Age (years), mean (95% CI)	59.9 (57.2–62.5)	70.0 (67.2–72.7)	<0.001
Male	111 (47)	69 (50)	NS
Underlying disease[b]	121 (51)	101 (74)	<0.001
Asthma	32 (14)	22 (16)	NS
COPD	51 (22)	49 (36)	0.003
Ischemic heart disease	38 (16)	39 (29)	0.004
Heart failure	20 (9)	28 (20)	0.001
Chronic renal failure	19 (8)	18 (13)	NS
Diabetes type I	3 (1)	0	NS
Diabetes type II	30 (13)	17 (12)	NS
Cerebrovascular disease	11 (5)	11 (8)	NS
Malignancy	8 (3)	18 (13)	<0.001
Severity scores, mean (95% CI)			
APACHE II score	8.64 (8.05–9.23)	12.62 (11.69–13.55)	<0.001
PSI score	2.58 (2.43–2.74)	3.42 (3.23–3.60)	<0.001
PSI value	71.40 (67.19–75.61)	94.86 (89.23–100.50)	<0.001
CURB-65	1.46 (1.37–1.55)	1.79 (1.65–1.93)	<0.001

APACHE, Acute Physiology and Chronic Health Evaluation; CAP, community-acquired pneumonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CURB-65, confusion, urea, respiratory rate, blood pressure, age ≥ 65; HCAP, healthcare-associated pneumonia; NS, not significant; PSI, pneumonia severity index.
[a]Data presented as *n* () unless otherwise stated.
[b]Underlying disease includes patients with at least one of the following: COPD, asthma, diabetes mellitus type I or II, ischemic heart disease, heart failure, chronic renal failure, cerebrovascular disease or malignancy.

Table IV. Comparison of treatment and outcomes.[a]

	CAP ($n = 236$)	HCAP ($n = 137$)	p value
Antimicrobial therapy			
Penicillins[b]	15 (6)	7 (5)	NS
Penicillin combinations[c]	153 (65)	78 (57)	NS
Cephalosporins[d]	25 (11)	26 (19)	0.023
Carbapenems[e]	4 (2)	1 (1)	NS
Macrolides[f]	24 (10)	10 (7)	NS
Quinolones[g]	2 (1)	6 (4)	NS
Other antimicrobials[h]	6 (3)	7 (5)	NS
Antivirals[i]	7 (3)	2 (1)	NS
β-Lactam plus macrolide	103 (43.6)	43 (31.4)	0.019
Ineffective initial therapy	4 (2)	8 (6)	NS[j]
Outcomes			
Length of stay (days), mean 95% CI	7.39 (6.7–8.1)	8.2 (7.5–9.0)	NS
ICU admission	21 (9)	11 (8)	NS
Mechanical ventilation	7 (3)	5 (4)	NS
In-house mortality	3 (1)	14 (10)	< 0.001

CAP, community-acquired pneumonia; CI, confidence interval; HCAP, healthcare-associated pneumonia; ICU, intensive care unit.
[a]Data expressed as n (%) unless otherwise noted.
[b]Amoxicillin, phenoxymethylpenicillin or cloxacillin.
[c]Amoxicillin plus clavulanic acid.
[d]Cefazolin, cefuroxime, ceftriaxone or ceftazidime.
[e]Meropenem.
[f] Erythromycin, clarithromycin or azithromycin.
[g]Ciprofloxacin.
[h]Clindamycin, doxycyclin, vancomycin or trimethoprim sulfamethoxazole.
[i]Oseltamivir.
[j]Cases lacking adequate data for determination of therapy effectiveness were censured from the statistical comparison ($n = 71$).

to receive ineffective initial therapy than CAP patients: (Table IV). Review of the cases found to have received ineffective therapy demonstrated that in four cases coverage for an atypical agent was lacking, in four cases *Strep. pneumoniae* or *H. influenzae* were resistant to the initial treatment, and in four cases other gram-negative bacteria (GNB) were found, against which the initial antibiotic was ineffective.

Rates of ICU admission or need for ventilation support did not differ statistically between the groups (Table IV). However, mortality was significantly higher in the HCAP group, a finding not explained by the difference in age between groups when examined with regression analysis (data not shown). Age and underlying diseases were included in a multinomial logistic regression analysis of mortality rates for both types of pneumonia and the combined group. When examining the combined patient group a significant correlation with mortality was found only for cerebrovascular disease (odds ratio (OR) = 5.69, 95% confidence interval (CI) = 1.35–23.99, $p = 0.018$). We analyzed immunosuppression as a risk factor for worse outcomes among HCAP patients but no significant difference was found.

A comparison of mortality predicted by prognostic scores to actual mortality showed that the CURB-65 score overestimated mortality among CAP patients (predicted mortality, 6%; actual mortality, 1%). Otherwise the mortality rates predicted by both PSI and CURB-65 did not differ significantly from the actual values in our study. We did not examine mortality predicted by APACHE II as most patients did not meet the prerequisite of requiring ICU care.

Four (24%) of those who died received intensive care. In nine cases (53%) therapy was limited by the treating physician within the first 48 h. In those who died, the mean age was 72 years. Fourteen patients had no established etiology, two had pneumonia due to *Strep. pneumoniae*, and one had *H. influenzae*. None of the fatal cases received ineffective initial therapy.

Discussion

We present the results of a prospective study comparing the characteristics and outcomes of CAP and HCAP in a setting of low prevalence of antimicrobial resistance. Our results verify that a large proportion of patients with pneumonia requiring hospital admission fulfill HCAP criteria. Previous prospective investigations indicated that HCAP cases constitute 17–29% of pneumonia admissions [4,7,11], while retrospective studies have shown 31–67% [3,5,6,20,21]. The HCAP group in our study constituted 37% ($n = 137$) of pneumonia admissions [2].

The wide range of HCAP prevalence found may be due to the difference in setting, patient populations, and criteria used to define HCAP.

We showed that patients in the HCAP group were older and were more likely to suffer from underlying disease compared with the CAP patients, both factors previously shown to be associated with worse prognosis [14]. In our analysis only cerebrovascular disease, which is a known predictor of worse prognosis, was independently correlated with increased mortality [14]. We did not find that adverse outcomes were increased among immunosuppressed HCAP patients. This analysis was complicated by varying degrees of immunosuppression, as well as potential confounding by factors such as age and underlying disease, in addition to the relatively low number of patients. It is also possible that high rates of effective initial antimicrobial therapy may have limited adverse outcomes among immunosuppressed patients in this study.

We evaluated participants using three different severity scores to predict mortality and disease severity. The PSI and CURB-65 scores were designed for CAP patients and the APACHE II score is intended for analysis of patients admitted to ICU and is not specific to pneumonia. Nonetheless both patient groups were evaluated with all three scores for comparison. While differences in underlying disease, age, and need for long-term nursing care are potential confounders in this comparison, all three severity scores predicted a worse outcome for the HCAP group. In our analysis both PSI and CURB-65 provided accurate predictions of mortality for HCAP patients, suggesting that the excess mortality in this group may be explained by factors already accounted for. It is important to note that these scoring systems are not designed to take type of pathogen or resistance directly into account, factors that may be of great clinical significance. Both PSI and CURB-65 performed well in our study, suggesting that these predictive tools might also be of use when determining whether to admit patients with HCAP. However, validation in settings with higher rates of resistance are needed before making such a recommendation.

In this study *Strep. pneumoniae* was the most common pathogen overall, found at a similar rate in both groups (Table III). This is similar to studies from Spain and Japan, while contrasting results have been reported from the USA [3–6,10,11]. Influenza was relatively common in our study but it should be noted that our study period partially coincided with the 2009 influenza H1N1 pandemic, the pandemic strain accounting for 22 (88%) of the influenza cases and temporally coinciding with the local epidemic. The H1N1v2009 influenza was less likely to infect older patients and thus was more common among patients with CAP [22]. *M. pneumoniae* was also more commonly found among the CAP patients, confirming its role as a community pathogen in younger patients [23].

In some previous studies *Staph. aureus* has been reported in up to 47% of cases of HCAP, with a large percentage due to MRSA [3.5]. Other studies indicate a lower prevalence, ranging from 2% to 20% of diagnosed cases [4,6,8,9]. It is notable that the studies reporting the highest occurrence of *Staph. aureus* in HCAP also reported an unusually high incidence of this pathogen in CAP. Our study does not implicate *Staph. aureus* as a major respiratory pathogen in Iceland. Furthermore, no MRSA cases were diagnosed, consistent with the still low incidence of MRSA in the country [24,25].

GNB are an important group of potentially MDR bacteria and previous studies indicate a relatively high incidence of these pathogens in HCAP. According to two recent studies from the USA, *Pseudomonas* accounted for 25% of HCAP with confirmed microbiological etiology [3,5]. Shindo et al. examined patients in a smaller hospital in Japan and found that gram-negative organisms accounted for 44% of diagnosed cases, of which *Pseudomonas* species accounted for 24% [6]. In contrast, two recent prospective investigations from Spain identified GNB among HCAP patients in only 5% and 6% of diagnosed cases, respectively [4,11]. In the present study 4% of HCAP patients were diagnosed with a GNB. None of the strains tested positive for extended-spectrum β-lactamase (ESBL) or ampC production. This is consistent with the overall low prevalence of antimicrobial resistance among this group of organisms in Iceland [26].

Previous studies have indicated that HCAP patients are more likely to receive inappropriate initial antibiotic therapy and that this may contribute to excess mortality [5,6,8]. In the present study HCAP patients were not more likely to receive inappropriate initial therapy compared with CAP patients (Table IV). No association was seen between inappropriate initial antimicrobial therapy and increased mortality. Inappropriate initial therapy was found less frequently than in previous studies [5,6], but the low number of cases found is a potential weakness in our analysis and increases the risk of a beta error. Additionally an etiologic agent was found less frequently among patients who died during hospitalization. It is possible that resistance rates were higher in this group but the overall low rates of resistance found in our study suggest that this is unlikely.

Mortality rates in this study were low in both groups when compared with some earlier retrospective studies [5–7] but similar to previous prospective study results [4,11]. The present study was

population-based and therefore included patients who are generally not referred to larger referral centers where some other published studies have been performed. The low incidence of resistant organisms in Iceland and in our center may also be a contributing factor [5–7,24].

Our results indicate that the broad antimicrobial treatment recommendations for HCAP outlined in current guidelines [2] do not apply in Iceland. These results are in all likelihood applicable in other low resistance settings. Local antimicrobial resistance patterns should be considered before advocating use of broad-spectrum antimicrobial therapy in patients with HCAP.

In summary, we included 94% of consecutive patients admitted with pneumonia from a geographically defined population over 1 year in this study. Our results confirmed that a large portion of pneumonia patients (37%) fulfill HCAP criteria. These patients had increased mortality in comparison with CAP patients, a finding not explained by the presence of MDR pathogens or inappropriate initial antimicrobial therapy. We propose that excess mortality in the HCAP group may primarily be due to patient factors such as more severe underlying diseases and co-morbidities. HCAP patients may be at an increased risk of carrying MDR pathogens, but local epidemiological resistance patterns should be the most important factor when selecting empiric antibiotic therapy in this patient group.

Acknowledgments

The authors wish to thank Janus F. Gudnason MD, Kristinn L. Hallgrimsson MD, Berglind Kristjansdottir MD, and Gunnsteinn Haraldsson PhD for their work in recruiting participants and processing clinical samples. We wish to thank the house staff, nurses, and laboratory personnel of Landspitali University Hospital for their assistance in recruiting participants and collecting and preserving samples.

Declaration of interest: This work was supported by grants from the Icelandic Center for Research, Rannís (grant no. 100436021), URL: http://rannis.is/english/home/, the Landspitali University Hospital Science Fund, and the University of Iceland Research Fund.

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