

Health Care–Associated Pneumonia Requiring Hospital Admission

Epidemiology, Antibiotic Therapy, and Clinical Outcomes

Jordi Carratalà, MD, PhD; Analia Mykietiuik, MD; Núria Fernández-Sabé, MD, PhD; Cristina Suárez, MD; Jordi Dorca, MD, PhD; Ricard Verdaguier, MD; Frederic Manresa, MD, PhD; Francesc Gudiol, MD, PhD

Background: Health care–associated pneumonia (HCAP) has been proposed as a new category of respiratory infection. However, limited data exist to validate this entity. We aimed to ascertain the epidemiology, causative organisms, antibiotic susceptibilities, and outcomes of and empirical antibiotic therapy for HCAP requiring hospitalization.

Methods: Observational analysis of a prospective cohort of nonseverely immunosuppressed hospitalized adults with pneumonia. Patients who had recent contact with the health care system through nursing homes, home health care programs, hemodialysis clinics, or prior hospitalization were considered to have HCAP.

Results: Of 727 cases of pneumonia, 126 (17.3%) were HCAP and 601 (82.7%) were community acquired. Compared with patients with community-acquired pneumonia, patients with HCAP were older (mean age, 69.5 vs 63.7 years; $P < .001$), had greater comorbidity (95.2% vs 74.7%; $P < .001$), and were more commonly classified into high-

risk pneumonia severity index classes (67.5% vs 48.8%; $P < .001$). The most common causative organism was *Streptococcus pneumoniae* in both groups (27.8% vs 33.9%). Drug-resistant pneumococci were more frequently encountered in cases of HCAP. *Legionella pneumophila* was less common in patients with HCAP (2.4% vs 8.8%; $P = .01$). Aspiration pneumonia (20.6% vs 3.0%; $P < .001$), *Haemophilus influenzae* (11.9% vs 6.0%; $P = .02$), *Staphylococcus aureus* (2.4% vs 0%; $P = .005$), and gram-negative bacilli (4.0% vs 1.0%; $P = .03$) were more frequent in HCAP. Patients with HCAP more frequently received an initial inappropriate empirical antibiotic therapy (5.6% vs 2.0%; $P = .03$). The overall case-fatality rate (< 30 days) was higher in patients with HCAP (10.3% vs 4.3%; $P = .007$).

Conclusions: At present, a substantial number of patients initially seen with pneumonia in the emergency department have HCAP. These patients require a targeted approach when selecting empirical antibiotic therapy.

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Author Affiliations: Infectious Disease Service (Drs Carratalà, Mykietiuik, Fernández-Sabé, Suárez, and Gudiol), Respiratory Service (Drs Dorca and Manresa), and Microbiology Service (Dr Verdaguier), Institut d'Investigació Biomèdica de Bellvitge–Hospital Universitari de Bellvitge, University of Barcelona, L'Hospitalet, Barcelona, Spain.

PNEUMONIAS HAVE TRADITIONALLY been classified as community or hospital acquired, and this classification is used to guide diagnosis and treatment decisions.¹⁻⁴ However, out-of-hospital care is becoming more complex, and an increasing number of patients now reside in nursing homes, receive outpatient parenteral therapy, attend hemodialysis clinics, and receive domiciliary care. Infections occurring among outpatients in contact with the health care system have recently been termed *health care–associated infections*.⁵ In an important study, Friedman et al have shown that health care–associated bloodstream infections are more similar to nosocomial infections than to community-acquired infections and require a targeted therapeutic approach.^{5,6} These investigators pointed out the need for studies to validate this new category

for infections other than bacteremias.⁵ Although health care–associated pneumonia (HCAP) has recently been proposed as a new category of respiratory infection,⁷ limited data exist to corroborate this assumption. Moreover, the definition of HCAP varies among studies and includes mixed patient populations. We sought to determine the epidemiology, causative organisms, antibiotic susceptibilities, and outcomes of and empirical antibiotic therapy for HCAP among a prospective cohort of patients requiring hospitalization.

METHODS

SETTING, PATIENTS, AND STUDY DESIGN

The study was conducted at a 900-bed university hospital for adults. All nonseverely immunosuppressed patients admitted to the hospital with pneumonia through the emergency

department from January 1, 2001, through December 31, 2004, were prospectively recruited and followed up. Patients with neutropenia and AIDS and who had undergone transplantation were not included.

Patients with pneumonia were classified into the following 2 groups: HCAP and community-acquired pneumonia (CAP). To classify patients into the HCAP group, we adapted the criteria described for bloodstream infection elsewhere.⁵ Therefore, patients had to fulfill any of the following:

1. Received intravenous therapy at home; received wound care or specialized nursing care through a health care agency, family, or friends; or had self-administered intravenous medical therapy in the 30 days before pneumonia. (Patients whose only home therapy was oxygen use were excluded.)
2. Attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the 30 days before pneumonia.
3. Were admitted to an acute care hospital for 2 or more days in the 90 days before pneumonia.
4. Resided in a nursing home or a long-term care facility.

Patients were classified into the CAP group if they did not fit the criteria for HCAP. We compared characteristics across groups.

This prospective, observational study was approved by the institutional review board, and informed consent was obtained from patients.

CLINICAL ASSESSMENT, ANTIBIOTIC THERAPY, AND FOLLOW-UP

Microbiological studies included 2 sets of blood cultures and sputum Gram stain and culture, when available. Urinary antigen detection for *Streptococcus pneumoniae* and *Legionella pneumophila* serogroup 1 was performed if indicated by the attending physician. Paired serum samples collected during the acute and convalescent phases of infection were obtained for serologic studies. To stratify patients into risk classes, we used the prediction rule, calculated according to the pneumonia severity index, as described elsewhere.⁸ The pneumonia severity index stratifies patients into 5 risk classes, with 30-day mortality ranging from 0.1% in class I to 27.0% in class V.

Antibiotic therapy was initiated in the emergency department in accordance with the hospital guidelines, which recommended the administration of a β -lactam (ceftriaxone sodium or amoxicillin and clavulanate potassium) with or without a macrolide (erythromycin ethylsuccinate or clarithromycin) or levofloxacin. Combination therapy was recommended for patients with clinical suspicion of a *Legionella* species or an atypical pathogen or in the absence of a demonstrative finding on sputum Gram stain results. Levofloxacin was allowed for selected cases and was recommended for patients with a urine antigen test result that was positive for *L pneumophila* serogroup 1. Combined amoxicillin-clavulanate was recommended for patients with clinical suspicion of aspiration pneumonia to provide adequate antianaerobic coverage.²

Patients were seen daily during their hospital stay by 1 or more of the investigators, who recorded clinical data in a computer-assisted protocol. Data were collected on demographic characteristics, comorbidities, causative organisms, antibiotic susceptibilities, empirical antibiotic therapy, and outcomes, including mortality. All assessments were made by means of a standard protocol. A long-term follow-up visit took place 1 month after discharge.

DEFINITIONS

Pneumonia was defined as the presence of a new infiltrate on a chest radiograph plus 1 or more of the following: fever (temperature $\geq 38.0^{\circ}\text{C}$) or hypothermia (temperature $< 35.0^{\circ}\text{C}$), new cough with or without sputum production, pleuritic chest pain, dyspnea, and altered breath sounds on auscultation.⁹

Prior antibiotic therapy was defined as use of any antibiotic for more than 48 hours during the previous 3 months.¹⁰ The diagnosis of septic shock was based on a systolic blood pressure of less than 90 mm Hg and peripheral hypoperfusion with clinical or bacteriologic evidence of uncontrolled infection.¹⁰

The appropriateness of antibiotic therapy was analyzed for all cases with an etiologic diagnosis according to susceptibility test criteria for lower respiratory tract pathogens, as previously described.¹¹ To define the appropriateness of therapy for pneumococcal pneumonia cases, we used the National Committee for Clinical Laboratory Standards criteria of 2000.¹² Patients who received amoxicillin (with or without clavulanate) or ceftriaxone and had *S pneumoniae* strains with intermediate resistance to amoxicillin (minimum inhibitory concentration [MIC] of 4 $\mu\text{g}/\text{mL}$) or ceftriaxone (MIC of 1 $\mu\text{g}/\text{mL}$) were considered to have received appropriate therapy.

Empirical antibiotic therapy was defined as antibiotics received on the first day of therapy for pneumonia. *Initial inappropriate therapy* was defined as the absence of antimicrobial agents directed at a specific type of organism or administration of an antibiotic to which the organism was resistant. Patients with aspiration pneumonia who had not received anti-aerobic coverage (ie, amoxicillin-clavulanate) were considered to have received an inappropriate empirical antibiotic therapy.

Complications were defined as any untoward circumstances occurring during hospitalization. *Early case-fatality rate* was defined as death from any cause within 48 hours of hospitalization. *Overall case-fatality rate* was defined as death from any cause within 30 days of hospitalization.

MICROBIOLOGICAL STUDIES

The investigation of pathogens in blood, normally sterile fluids, sputum, and other samples was performed by standard microbiological procedures. The finding of the *S pneumoniae* antigen in urine was detected by using a rapid immunochromatographic assay (NOW Assay; Binax Inc, Portland, Maine). *Legionella pneumophila* serogroup 1 antigen in urine was detected by an immunochromatographic method (NOW *Legionella* Urinary Antigen Test; Binax Inc). Standard serologic methods were used to determine antibodies against atypical agents. The antibiotic sensitivity of all isolates was determined by using a microdilution panel (STRHAE1, Sensititre; Trek Diagnostic Systems Ltd, West Sussex, England) according to the National Committee for Clinical Laboratory Standards guidelines.¹³ We used the National Committee for Clinical Laboratory Standards criteria to define the penicillin susceptibility of pneumococcal isolates.¹²

ETIOLOGIC DIAGNOSIS

An etiologic diagnosis was considered definitive in the following situations: isolation of a respiratory pathogen in a usually sterile specimen, isolation of *L pneumophila* in sputum, detection of *L pneumophila* serogroup 1 or pneumococcal antigen in urine, 4-fold increase in the antibody titer, or seroconversion for atypical pathogens. An etiologic diagnosis was considered presumptive when a predominant microorganism was isolated from a purulent sample (presence of > 25 polymorphonuclear leukocytes and < 10 squamous cells per low-power field [original magnification $\times 10$]) with compatible Gram

stain findings. Presumptive aspiration pneumonia was diagnosed on a clinical and radiological basis in patients who had risk factors such as compromised consciousness, altered gag reflex, dysphagia, severe periodontal disease, putrid sputum, and radiographic evidence of involvement of a dependent pulmonary segment or necrotizing pneumonia. Cases that did not meet any of the above criteria were considered pneumonias of unknown etiology.

STATISTICAL ANALYSIS

The results were analyzed using a commercially available statistical software package (SPSS, version 11.5; SPSS Inc, Chicago, Illinois). To detect significant differences between groups, we used the χ^2 or Fisher exact test for categorical variables, and the 2-tailed *t* test or Mann-Whitney test for continuous variables, when appropriate. Statistical significance was established at $\alpha = .05$. All reported *P* values are 2-tailed.

RESULTS

PATIENT CHARACTERISTICS

During the study period, 727 consecutive adults with pneumonia were hospitalized; 126 (17.3%) had HCAP and 601 (82.7%) had CAP. Fifty-five of the 126 patients (43.7%) in the HCAP group had been admitted to an acute care hospital for 2 or more days in the 90 days before pneumonia; 40 (31.7%) attended a hospital or a hemodialysis clinic or received intravenous chemotherapy in the 30 days before pneumonia; 32 (25.4%) resided in a nursing home or a long-term care facility; and 18 (14.3%) received home health care. Nineteen patients fulfilled more than 1 criterion to be included in the HCAP group.

The characteristics of patients with HCAP and CAP are compared in **Table 1**. Patients with HCAP were older, had greater comorbidity, and were more commonly classified into high-risk pneumonia severity index classes than were patients with CAP. Comorbid conditions significantly associated with HCAP were chronic obstructive pulmonary disease, chronic heart disease, cerebrovascular disease, and cancer. Impaired consciousness at presentation was more frequent in patients with HCAP.

CAUSATIVE ORGANISMS AND ANTIBIOTIC SUSCEPTIBILITIES

An etiologic diagnosis was more frequently established in patients with HCAP than in those with CAP (67.5% vs 56.1%; *P* = .02). **Table 2** shows the distribution of causative organisms in both groups. Overall, *S pneumoniae* was the most frequent causative pathogen. Results of the urine antigen test were positive in 76.0% and 88.2% of patients, respectively. Aspiration pneumonia was significantly more frequent in patients with HCAP, whereas *L pneumophila* was less commonly identified as the causative organism in this group. *Haemophilus influenzae*, *Staphylococcus aureus*, and gram-negative bacilli were more frequently documented as causative organisms in patients with HCAP.

Table 1. Main Clinical Characteristics of Hospitalized Patients With Pneumonia by Epidemiological Group

Characteristic	HCAP Group (n = 126) ^a	CAP Group (n = 601) ^a	<i>P</i> Value
Age, mean ± SD, y	69.5 ± 15.0	63.7 ± 17.1	< .001
Male sex	95 (75.4)	420 (69.9)	.23
Comorbid conditions ^b	120 (95.2)	449 (74.7)	< .001
COPD	47 (37.3)	151 (25.1)	.005
Chronic heart disease	45 (35.7)	161 (26.8)	.04
Diabetes mellitus	20 (15.9)	100 (16.6)	.83
Cerebrovascular disease	38 (30.1)	71 (11.8)	< .001
Cancer	19 (15.1)	28 (4.7)	< .001
Chronic renal failure	8 (6.3)	20 (3.3)	.13
Chronic liver disease	3 (2.4)	22 (3.7)	.60
Autoimmune disease	2 (1.6)	8 (1.3)	.82
Other	6 (4.8)	29 (4.8)	.98
Long-term corticosteroid use	15 (11.9)	25 (4.2)	.002
Smoking	29 (23.0)	159 (26.5)	.45
Heavy drinking	20 (15.9)	103 (17.1)	.77
Influenza vaccine (season)	65 (51.6)	232 (38.6)	.001
Pneumococcal vaccine, 5 y	31 (24.6)	102 (17.0)	.02
Previous antibiotic therapy	36 (28.6)	29 (4.8)	< .001
Impaired consciousness	25 (19.8)	64 (10.6)	.004
Septic shock at onset	6 (4.8)	30 (5.0)	.91
Respiratory failure (PaO ₂ < 60 mm Hg or PaO ₂ /FiO ₂ < 300 mm Hg)	51 (40.5)	259 (43.1)	.73
Multilobar infiltrates	40 (31.7)	193 (32.1)	.96
Plural effusion	24 (19.0)	113 (18.8)	.94
PSI risk classes ^c			< .001
Low risk	41 (32.5)	308 (51.2)	
High risk	85 (67.5)	293 (48.8)	

Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; FiO₂, fraction of inspired oxygen; HCAP, health care-associated pneumonia; PSI, pneumonia severity index. ^aData are given as number (percentage) except where otherwise indicated. ^bFifty-seven patients in the HCAP group and 155 patients in the CAP group had more than 1 comorbid condition. ^cPatients were stratified into the following risk classes according to the PSI score: low risk (≤ 90 points, classes I, II, and III) and high risk (> 90 points, classes IV and V).

Bacteremia occurred in 11 patients with HCAP (*S pneumoniae* in 7, *Pseudomonas aeruginosa* in 2, and *Escherichia coli* in 2) and in 65 patients with CAP (*S pneumoniae* in 59, *H influenzae* in 2, *P aeruginosa* in 1, *E coli* in 2, and *Klebsiella pneumoniae* in 1). The occurrence of bacteremia was similar in both groups of patients (8.7% vs 10.6%; *P* = .52). Bacteremia due to gram-negative bacilli was more frequent in patients with HCAP (3.2% vs 0.7%; *P* = .01).

Penicillin-resistant pneumococcal strains were more commonly isolated from patients with HCAP (33.3% vs 14.9%; *P* = .04). The MICs of penicillin-resistant strains ranged from 0.12 to 4.0 µg/mL in both groups. No differences were found regarding the rates of resistance to ceftriaxone (4.2% vs 3.5%; *P* > .99) (MIC, 2 µg/mL). Resistance to erythromycin was most frequent in patients with HCAP (41.7% vs 15.8%; *P* = .009). The MIC was more than 256 µg/mL for all but 2 (MIC, 16 µg/mL) erythromycin-resistant strains. Only 1 pneumococcal strain, which was isolated from a patient with HCAP, was resistant to levofloxacin (MIC, 16 µg/mL).

Among *H influenzae* strains, β-lactamase production was detected in 20.0% of isolates from patients with HCAP

Table 2. Etiology in 727 Cases of Pneumonia by Epidemiological Group

Etiology	Epidemiological Group by Diagnosis						P Value
	HCAP (n = 126)			CAP (n = 601)			
	Presumptive, No. of Patients	Definitive, No. of Patients	Total, No. (%) ^a	Presumptive, No. of Patients	Definitive, No. of Patients	Total, No. (%) ^a	
<i>Streptococcus pneumoniae</i>	11	24	35 (27.8)	34	170	204 (33.9)	.18
<i>Legionella pneumophila</i>	0	3	3 (2.4)	0	53	53 (8.8)	.01
<i>Haemophilus influenzae</i>	15	0	15 (11.9)	34	2	36 (6.0)	.02
Aspiration pneumonia ^b	23	3	26 (20.6)	15	3	18 (3.0)	<.001
Gram-negative bacilli	1	4	5 (4.0)	2	4	6 (1.0)	.03
<i>Pseudomonas aeruginosa</i>	0	2	2 (1.6)	2	1	3 (0.5)	
<i>Escherichia coli</i>	1	2	3 (2.4)	0	2	2 (0.3)	
<i>Klebsiella pneumoniae</i>	0	0	0	0	1	1 (0.2)	
<i>Staphylococcus aureus</i>	3	0	3 (2.4)	0	0	0	.005
Atypical agents	0	2	2 (1.6)	0	22	22 (3.7)	.24
<i>Chlamydomphila pneumoniae</i>	0	0	0	0	5	5 (0.8)	
<i>Mycoplasma pneumoniae</i>	0	1	1 (0.8)	0	12	12 (2.0)	
<i>Coxiella burnetii</i>	0	1	1 (0.8)	0	7	7 (1.2)	
Other organisms ^c	2	2	4 (3.2)	3	7	10 (1.7)	.26
No pathogen identified	41 (32.5)	264 (43.9)	.02

Abbreviations: CAP, community-acquired pneumonia; HCAP, health care-associated pneumonia; ellipses, not applicable.

^aPercentages total more than 100% owing to 8 patients (6.3%) with HCAP and 9 patients with CAP (1.5%) who had mixed pneumonias.

^b*Streptococcus anginosus* group (n=3), *Eubacterium lentum* (n=1), and *Enterobacter cloacae* (n=1) were isolated from pleural fluid in 3 patients with HCAP, and *S anginosus* group (n=1), *Prevotella bivia* (n=1), and *Porphyromonas asaccharolytica* (n=1) were isolated from pleural fluid in 3 patients with CAP.

^cOther causative organisms were *Moraxella catarrhalis* (n = 2), influenza A virus (n=1), and adenovirus (n=1) in the HCAP group and varicella-zoster virus (n=6), *M catarrhalis* (n=2), influenza A virus (n=1), and *Neisseria meningitidis* (n=1) in the CAP group.

and in 9.7% of isolates from patients with CAP (P=.38). One of 3 *S aureus* strains causing HCAP was methicillin resistant. No gram-negative bacilli produced extended-spectrum β -lactamases.

ANTIBIOTIC THERAPY AND CLINICAL OUTCOMES

In accordance with our hospital guidelines, most patients received adequate initial empirical antibiotic therapy (**Table 3**). No differences were found regarding the mean \pm SD time to institution of initial antibiotic therapy (door-to-needle time) between groups (4.53 \pm 4.25 vs 4.36 \pm 3.72 hours; P=.64). Patients with HCAP more frequently received an inappropriate initial empirical antibiotic therapy than did patients with CAP. Causes of pneumonia among patients receiving an inappropriate initial antibiotic therapy were aspiration pneumonia (4 cases), *P aeruginosa* (2 cases), and methicillin-resistant *S aureus* (1 case) in the HCAP group, and *L pneumophila* (6 cases), atypical agents (3 cases), aspiration pneumonia (2 cases), and *P aeruginosa* (1 case) in the CAP group.

As shown in Table 3, there were no differences between groups regarding the development of in-hospital complications. Similar percentages of patients in the 2 groups required intensive care unit (ICU) admission and underwent mechanical ventilation. No differences were found in causative organisms between non-ICU-admitted patients with HCAP and ICU-admitted patients with HCAP. The median length of hospital stay was significantly longer for patients with HCAP.

The early and overall case-fatality rates were higher in patients with HCAP. Causes of death were respiratory failure (8 of 13 patients in the HCAP group and 15 of 26 patients in the CAP group), shock/multiorgan failure (4 of 13 and 9 of 26 patients, respectively), and congestive heart failure (1 of 13 and 2 of 26 patients, respectively). Among patients who received an initial inappropriate empirical therapy, one patient with HCAP died of septic shock (*P aeruginosa*) and another died of acute respiratory failure (methicillin-resistant *S aureus*).

COMMENT

This prospective study shows that a substantial number of patients currently hospitalized with pneumonia have had recent contact with the health care system through nursing homes, home health care programs, hemodialysis clinics, or hospitalization. Compared with patients with CAP, patients with HCAP were older, had more comorbid conditions, and were more commonly classified into high-risk pneumonia severity index classes. We also documented significant differences in the spectrum of causative organisms and antibiotic susceptibilities between the 2 pneumonia groups. Indeed, patients with HCAP more frequently received an initial inappropriate empirical antibiotic therapy and had higher case-fatality rates.

In recent years, dramatic changes in the health care system have shifted a considerable part of patient care from the hospitals to the community. As a result, the traditional distinction between community- and hospital-acquired infections has become less clear, with some in-

Table 3. Antibiotic Therapy and Outcomes of Pneumonia by Epidemiological Group

Therapy and Outcomes	HCAP Group (n = 126) ^a	CAP Group (n = 601) ^a	P Value
Initial antibiotic therapy			.07
Monotherapy	95 (75.4)	408 (67.9)	
β-Lactams	78 (61.9)	252 (41.9)	
Quinolones	13 (10.3)	152 (25.3)	
Other	4 (3.2)	4 (0.7)	
Combination therapy	31 (24.6)	193 (32.1)	
β-Lactams + quinolones	27 (21.4)	169 (28.1)	
β-Lactams + macrolides	4 (3.2)	10 (1.7)	
Other combinations	0	14 (2.3)	
Inappropriate antibiotic therapy	7 (5.6)	12 (2.0)	.03
In-hospital complications	35 (27.8)	149 (24.8)	.48
ICU admission	8 (6.3)	52 (8.7)	.39
Need for mechanical ventilation	4 (3.2)	28 (4.7)	.48
Length of hospital stay, median (IQR), d ^b	9 (7.0-13.0)	8 (6.0-11.0)	.003
Length of intravenous therapy, mean ± SD, d ^b	4.8 ± 3.4	4.1 ± 3.0	.051
Length of therapy, mean ± SD, d ^b	10.4 ± 3.4	10.4 ± 4.7	.94
Early case-fatality rate, < 48 h	4 (3.2)	5 (0.8)	.053
Overall case-fatality rate, < 30 d	13 (10.3)	26 (4.3)	.007

Abbreviations: CAP, community-acquired pneumonia; HCAP, health care–associated pneumonia; ICU, intensive care unit; IQR, interquartile range.

^aData are given as number (percentage) except where otherwise indicated.

^bPatients who died within 48 hours of hospitalization were excluded from these analyses.

fections having mixed characteristics of both types of acquisition. In this regard, the term *health care–associated pneumonia* has recently been suggested to describe this patient population.^{7,14} However, as shown in 2 recent reviews dealing with HCAP,^{15,16} there is limited information to validate this new clinical entity. In fact, most available data come from studies involving hospitalized patients with ventilator-associated pneumonia and nonintubated patients with hospital-acquired pneumonia (HAP).¹⁷⁻¹⁹ Conversely, little is known about the bacteriology and clinical outcomes of HCAP arising in the community. In a retrospective study conducted in the United States and taken from a large multi-institutional database, Kollef et al²⁰ examined rates of CAP, HCAP, ventilator-associated pneumonia, and HAP. Approximately 50% of patients had CAP and more than 20% had HCAP, with *S aureus* being a major causative pathogen.

We found that *S pneumoniae* was the most frequent causative organism in both pneumonia groups. In recent years, the emergence of multidrug-resistant pneumococci has become a therapeutic challenge for clinicians worldwide.²¹ The prior use of antimicrobials, which in our study was more frequent in patients with HCAP, is a well-known risk factor for antibiotic resistance.²² In this regard, we found that patients with HCAP had higher rates of resistance to penicillin and erythromycin than did patients with CAP. The only case of levofloxacin-resistant *S pneumoniae* also occurred in a patient with HCAP, who was initially treated with this drug and failed to respond.

We found that aspiration pneumonia was significantly more frequent in patients with HCAP than in patients with CAP. Patients with HCAP were older and more often had cerebrovascular diseases and impaired consciousness at presentation. Difficulty swallowing is

relatively common among patients with these conditions, and it has been shown that they are more prone to aspiration. In our study, aspiration pneumonia was a frequent cause of receiving inappropriate empirical antibiotic therapy among patients with HCAP. The recognition of aspiration pneumonia requires a careful clinical evaluation when macroscopic aspiration is not observed.²³ Moreover, the results of microbiological studies are often negative because the invasive techniques necessary to obtain a reliable diagnosis are not usually performed. Therefore, the real incidence of aspiration pneumonia may have been underestimated in previous studies, in which no case of aspiration pneumonia was documented.²⁰

In our study, although *L pneumophila* represented the second most frequent cause of CAP, it accounted for only 2.4% of HCAP episodes. The low prevalence of *Legionella* pneumonia in our study may be owing to a less frequent exposure to exogenous sources. Nevertheless, the potential relevance of *L pneumophila* as a cause of ventilator-assisted pneumonia and HAP occurring in nonintubated patients should not be dismissed whenever the hospital water supply is colonized by this organism.²⁴

In our study, the incidence of *S aureus* as a cause of HCAP was low and was similar to the figure documented in previous studies that included nonintubated patients with HAP.^{18,19} The most striking difference when we compared our results with those of Kollef et al²⁰ was that in their study *S aureus* caused 46.7% of HCAP and 47.1% of HAP episodes. Surprisingly, it was also the most frequent pathogen in CAP (25.5%). As has been pointed out,¹⁶ data from this study were retrospectively retrieved from a database without the use of uniform criteria for distinguishing colonizing bacteria from pathogens. Moreover, 50% of

pneumonia cases occurred in nursing homes and long-term care facilities.

We found that *H influenzae* and other gram-negative bacilli were more frequent in the HCAP group than in the CAP group. Indeed, gram-negative bacteremia occurred more commonly among patients with HCAP. Although β -lactamase production was more frequent among strains isolated from patients with HCAP, no gram-negative bacilli produced extended-spectrum β -lactamases. In fact, no multidrug-resistant gram-negative bacilli were documented in our study. Nowadays, patients admitted to the ICU who develop late-onset ventilator-assisted pneumonia are at the greatest risk for colonization and infection with multidrug-resistant bacterial pathogens.^{7,14,15} However, infections due to extended-spectrum β -lactamase-producing *E coli* are steadily increasing in many countries.^{25,26}

We found that patients with HCAP were more frequently given an inappropriate initial empirical antibiotic therapy than were those with CAP ($P=.03$). In our study, the length of hospital stay was significantly longer for patients with HCAP ($P=.003$), who also had higher overall case-fatality rates than did patients with CAP ($P=.007$). Our findings concur with those reported by Kollef et al,²⁰ suggesting that failure to treat serious infections with appropriate antimicrobial agents at the onset may be associated with an increase in patient morbidity and mortality.

Currently, we believe that ertapenem sodium offers adequate coverage for the subset of patients with HCAP who require evaluation in the emergency department and hospitalization. We concur with Yakovlev et al²⁷ in that empirical antibiotic therapy directed against *Pseudomonas* species may not be routinely needed for this segment of patients with HCAP acquired outside an ICU unless they have received broad-spectrum antibiotics during the previous few months.

Finally, our prospective observational study has certain limitations that should be acknowledged. The research was performed in a single institution and the number of patients with HCAP was relatively small. Therefore, our results should be interpreted with caution because different rates of antibiotic resistance among respiratory pathogens can be encountered in other countries.

Our study results suggest that HCAP should be regarded as a separate category of respiratory infection. According to our data, physicians dealing with patients with pneumonia in the emergency department should be aware that a substantial number of patients presenting with pneumonia may have HCAP and require a targeted approach when selecting empirical antibiotic therapy. Further research involving a large number of patients from different institutions and geographic areas is warranted to confirm our findings regarding antibiotic resistance.

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Correspondence: Jordi Carratalà, MD, PhD, Infectious Disease Service, Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907 L'Hospitalet, Barcelona, Spain (jcarratala@ub.edu).

Author Contributions: *Study concept and design:* Carratalà and Gudiol. *Acquisition of data:* Carratalà, Mykietiuik,

Fernández-Sabé, Suárez, Dorca, Verdaguer, and Gudiol. *Analysis and interpretation of data:* Carratalà, Mykietiuik, Fernández-Sabé, Suárez, Dorca, Manresa, and Gudiol. *Drafting of the manuscript:* Carratalà and Mykietiuik. *Critical revision of the manuscript for important intellectual content:* Carratalà, Mykietiuik, Verdaguer, Manresa, and Gudiol. *Statistical analysis:* Mykietiuik. *Obtained funding:* Carratalà, Dorca, and Gudiol. *Administrative, technical, and material support:* Verdaguer. *Study supervision:* Carratalà, Fernández-Sabé, Suárez, Manresa, and Gudiol.

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REFERENCES

1. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia. *Clin Infect Dis*. 2000;31(2):347-382.
2. Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis*. 2003;37(11):1405-1433.
3. Niederman MS, Mandell LA, Anzueto A, et al. Guidelines for the management of adults with community-acquired pneumonia: diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med*. 2001;163(7):1730-1754.
4. Fagon JY, Chastre J. Antimicrobial treatment of hospital-acquired pneumonia. *Clin Chest Med*. 2005;26(1):97-104.
5. Friedman ND, Kaye KS, Stout JE, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med*. 2002;137(10):791-797.
6. McDonald JR, Friedman D, Stout JE, Sexton DJ, Kaye KS. Risk factors for ineffective therapy in patients with bloodstream infection. *Arch Intern Med*. 2005;165(3):308-313.
7. American Thoracic Society Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388-416.
8. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243-250.
9. Carratalà J, Fernández-Sabé N, Ortega L, et al. Outpatient care compared with hospitalization for community-acquired pneumonia: a randomized trial in low-risk patients. *Ann Intern Med*. 2005;142(3):165-172.
10. Mykietiuik A, Carratalà J, Domínguez A, et al. Effect of prior pneumococcal vaccination on clinical outcome of hospitalized adults with community-acquired pneumococcal pneumonia. *Eur J Clin Microbiol Infect Dis*. 2006;25(7):457-462.
11. Rosón B, Carratalà J, Fernández-Sabé N, Tubau F, Manresa F, Gudiol F. Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. *Arch Intern Med*. 2004;164(5):502-508.
12. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing: Tenth Informational Supplement (Aerobic Dilution)*. Wayne, PA: National Committee for Clinical Laboratory Standards; 2000. Document M100-S10 (M7).
13. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically: Approved Standard Fifth Edition*. Wayne, PA: National Committee for Clinical Laboratory Standards; 2000. Document M7-A5; supplemental tables M100-S10.

14. Tablan OC, Anderson JL, Besser R, et al; Healthcare Infection Control Practices Advisory Committee. Guidelines for preventing health-care-associated pneumonia: 2003 recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. *MMWR Recomm Rep*. 2004;53(RR-3):1-36.
15. Craven DE. What is healthcare-associated pneumonia, and how should it be treated? *Curr Opin Infect Dis*. 2006;19(2):153-160.
16. Fujitani S, Yu VL. A new category—healthcare-associated pneumonia: a good idea, but problems with its execution. *Eur J Clin Microbiol Infect Dis*. 2006;25(10):627-631.
17. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002;165(7):867-903.
18. Dorca J, Manresa F, Esteban L, et al. Efficacy, safety, and therapeutic relevance of transthoracic aspiration with ultrathin needle in nonventilated nosocomial pneumonia. *Am J Respir Crit Care Med*. 1995;151(5):1491-1496.
19. Sopena N, Sabria M; Neunos 2000 Study Group. Multicenter study of hospital-acquired pneumonia in non-ICU patients. *Chest*. 2005;127(1):213-219.
20. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest*. 2005;128(6):3854-3862.
21. Baddour LM, Yu VL, Klugman KP, et al. Combination therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med*. 2004;170(4):440-444.
22. Pallares R, Gudiol F, Liñares J, et al. Risk factors and response to antibiotic therapy in adults with bacteremic pneumonia caused by penicillin-resistant pneumococci. *N Engl J Med*. 1987;317(1):18-22.
23. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*. 2001;344(9):665-671.
24. Sabria M, Yu VL. Hospital-acquired legionellosis: solutions for a preventable infection. *Lancet Infect Dis*. 2002;2(6):368-373.
25. Rodríguez-Baño J, Navarro MD, Romero L, et al. Bacteremia due to extended-spectrum β -lactamase-producing *Escherichia coli* in the CTX-M era: a new clinical challenge. *Clin Infect Dis*. 2006;43(11):1407-1414.
26. Peña C, Gudiol C, Tubau F, et al. Risk-factors for acquisition of extended-spectrum β -lactamase-producing *Escherichia coli* among hospitalised patients. *Clin Microbiol Infect*. 2006;12(3):279-284.
27. Yakovlev SV, Strachounski LS, Woods GL, et al. Ertapenem versus cefepime for initial empirical treatment of pneumonia acquired in skilled-care facilities or in hospitals outside the intensive care unit. *Eur J Clin Microbiol Infect Dis*. 2006;25(10):633-641.