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Health Care-Associated Pneumonia and Community-Acquired Pneumonia: a Single-Center Experience[▽]

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Pneumonia occurring outside of the hospital setting has traditionally been categorized as community-acquired pneumonia (CAP). However, when pneumonia is associated with health care risk factors (prior hospitalization, dialysis, residing in a nursing home, immunocompromised state), it is now more appropriately classified as a health care-associated pneumonia (HCAP). The relative incidences of CAP and HCAP among patients requiring hospital admission is not well described. The objective of this retrospective cohort study, involving 639 patients with culture-positive CAP and HCAP admitted between 1 January 2003 and 31 December 2005, was to characterize the incidences, microbiology, and treatment patterns for CAP and HCAP among patients requiring hospital admission. HCAP was more common than CAP (67.4% versus 32.6%). The most common pathogens identified overall included methicillin-resistant *Staphylococcus aureus* (24.6%), *Streptococcus pneumoniae* (20.3%), *Pseudomonas aeruginosa* (18.8%), methicillin-sensitive *Staphylococcus aureus* (13.8%), and *Haemophilus influenzae* (8.5%). The hospital mortality rate was statistically greater among patients with HCAP than among those with CAP (24.6% versus 9.1%; $P < 0.001$). Administration of inappropriate initial antimicrobial treatment was statistically more common among HCAP patients (28.3% versus 13.0%; $P < 0.001$) and was identified as an independent risk factor for hospital mortality. Our study found that the incidence of HCAP was greater than that of CAP among patients with culture-positive pneumonia requiring hospitalization at Barnes-Jewish Hospital. Patients with HCAP were more likely to initially receive inappropriate antimicrobial treatment and had a greater risk of hospital mortality. Health care providers should differentiate patients with HCAP from those with CAP in order to provide more appropriate initial antimicrobial therapy.

Pneumonia developing outside of the hospital setting has traditionally been classified as community-acquired pneumonia (CAP). Nosocomial pneumonia refers to infections acquired during hospitalization and has been further differentiated into ventilator-associated pneumonia if pneumonia developed during the course of mechanical ventilation and hospital-acquired pneumonia if infection was not associated with mechanical ventilation (5). Health care-associated pneumonia (HCAP) is a relatively new category of nosocomial pneumonia that refers to infections that occur prior to hospital admission in patients with specific risk factors (immunosuppression, recent hospitalization, residence in a nursing facility, requiring dialysis) (5, 10). Categorization as HCAP is not due to the provision of health care per se but to exposure to environments within which reservoirs of infection exist (e.g., prior hospitalization, nursing homes, dialysis clinics). Patients with HCAP are usually infected with potentially antibiotic-resistant bacteria (methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter* species), while CAP is typically attributed to more-susceptible bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Legionella* species) (10, 14).

The relative incidences of CAP and HCAP among patients admitted to the hospital setting for pneumonia have not previously been systematically evaluated. Therefore, we performed a study with two goals. Our first goal was to determine the relative incidences of culture-positive CAP and HCAP in an urban teaching hospital. The second goal of this study was to examine the pathogens associated with culture-positive CAP and HCAP and the relative numbers of occurrences of inappropriate initial antimicrobial treatment.

MATERIALS AND METHODS

Study design. A retrospective cohort analysis of all culture-positive patients admitted to Barnes-Jewish Hospital (a 1,200-bed urban teaching hospital) with a diagnosis of pneumonia between 1 January 2003 and 31 December 2005 was performed.

Data source. One of the investigators (R. M. Reichley) identified all study patients by the presence of either a primary or secondary International Classification of Diseases, Ninth Revision, Clinical Modification code indicative of pneumonia and a concomitant positive respiratory bacterial culture, blood culture, or urine antigen test specific for *Legionella pneumophila* serogroup 1. The study database was constructed by merging patient-specific data from the automated hospital records, microbiology database, and pharmacy database of Barnes-Jewish Hospital.

Definitions. CAP was defined as a diagnosis of pneumonia in patients who did not meet any of the criteria for HCAP. The clinical diagnoses of CAP and HCAP had to be established within 48 h of hospitalization so that confirmatory respiratory cultures were obtained. Two of the following clinical criteria were required: fever (>38.3°C) or hypothermia (≤36.0°C), leukocytosis ($>10 \times 10^9$ cells/liter) or leukopenia ($\leq 4 \times 10^9$ cells/liter), or purulent tracheal aspirate or sputum. HCAP was defined as a diagnosis of pneumonia in patients admitted to the hospital who met at least one of the following criteria: (1) admission from a nursing home, rehabilitation hospital, or other long-term nursing care facility; (2)

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previous hospitalization within the immediately preceding 12 months; (3) receiving outpatient hemodialysis, peritoneal dialysis, or infusion therapy necessitating regular visits to a hospital-based clinic; or (4) having an immunocompromised state. This definition for HCAP was based on our prior experience with health care-associated infections (10, 16, 18).

The diagnosis of pneumonia was verified by one of the investigators (M. H. Kollef or K. E. Kollef) from the medical records and required the presence of a new radiographic infiltrate plus at least two of the following: (1) a white blood cell count of greater than $10{,}000 \times 10^3$/ml; (2) a temperature of ≥38.3°C; (3) purulent secretions from the lower respiratory tract; or (4) a ratio of the partial pressure of arterial oxygen to the inspired fraction of oxygen (PaO_2/FiO_2) of less than 300. Acceptable positive culture specimens included sputum, tracheal aspirate, bronchoscopic or blind bronchoalveolar lavage fluid, or blood. Blood cultures were accepted if the same microorganism was identified in a respiratory specimen and no other source for the positive blood culture could be identified. Additionally, a positive urine antigen for *Legionella* species qualified as a culture-positive specimen.

Antimicrobial treatment was classified as being inappropriate if the initially prescribed antibiotics were not active against the identified pathogens based on in vitro susceptibility testing. Appropriate antimicrobial treatment had to be prescribed within 24 h of hospital admission. The antimicrobial regimens employed at Barnes-Jewish Hospital for the treatment of suspected community-acquired pneumonia are ceftriaxone plus azithromycin or moxifloxacin monotherapy. All antimicrobial agents prescribed for CAP and HCAP, as well as for other infections at Barnes-Jewish Hospital, are also administered at adequate doses and intervals of administration, as monitored by the pharmacy department and as described previously (5–7, 9, 16). The community phenotype of methicillin-resistant *Staphylococcus aureus* was defined as isolates resistant to methicillin but sensitive to three or more of the following antibiotics: gentamicin, ciprofloxacin, trimethoprim-sulfamethoxazole, and clindamycin.

The definition of immunosuppression included the following: (1) daily administration of corticosteroids (at least 5 mg per day of prednisone or an equivalent drug), (2) seropositivity for human immunodeficiency virus, (3) having received either a solid organ transplant or bone marrow transplant, (4) treated with radiation therapy or chemotherapy for an underlying malignancy during the 6 months prior to hospital admission, and (5) having an underlying acquired immune deficiency disorder (hypogammaglobulinemia, combined variable immunodeficiency).

Data analysis. All comparisons were unpaired, and all tests of significance were two tailed. Continuous variables were compared, using the Student *t* test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. The chi-square or Fisher's exact test was used to compare categorical variables. We performed multiple logistic-regression analysis using SPSS software, version 11.0, for Windows (SPSS, Inc., Chicago, IL). Multivariate analysis was performed using models that were judged a priori to be clinically sound. This was prospectively determined to be necessary to avoid producing spuriously significant results with multiple comparisons. All potential risk factors significant at the 0.2 level in univariate analyses were entered into the model.

RESULTS

Patient characteristics. A total of 639 culture-positive patients with pneumonia were admitted to Barnes-Jewish Hospital during the study period. The mean age of the population was 58.9 ± 18.1 (range, 17 to 102); there were 356 (55.7%) males and 283 (44.3%) females. There were 431 (67.4%) patients classified as having HCAP and 208 (32.6%) with CAP. The characteristics of the patients with HCAP and CAP are provided in Table 1. Hospitalization during the previous 12 months was the most common criterion for HCAP. Most patients meeting the criteria for HCAP were previously hospitalized within 90 days of their current admission (Table 1). Patients with HCAP were significantly more likely to require mechanical ventilation and admission to the intensive care unit than patients with CAP.

Pathogen distribution. The microbiologic diagnosis of pneumonia was most often established by sputum culture or tracheal aspirate culture in 450 patients (CAP, 132 [63.5%] versus HCAP, 318 [73.8%]), blood cultures in 211 patients (CAP, 78 [37.5%] versus HCAP, 133 [30.9%]), bronchoalveolar lavage fluid cultures in 30 patients (CAP, 9 [4.3%] versus HCAP, 21 [4.9%]), and a positive urine antigen for *Legionella pneumophila* serogroup 1 in 8 patients (CAP, 7 [3.4%] versus HCAP, 1 [0.2%]).

TABLE 1. Patient characteristics[a]

Characteristic	No. (%) of patients with indicated infection		*P* value
	CAP (n = 208)	HCAP (n = 431)	
Age (yr)	57.0 ± 16.9	59.8 ± 18.5	0.072
Sex			
Male	121 (58.2)	235 (54.8)	0.418
Female	87 (42.8)	196 (46.2)	
Race			
White	100 (48)	273 (63.3)	<0.001
Black	106 (51)	158 (36.7)	
Other	2 (1)	0	
HCAP criteria			
Recent hospitalization		402 (93.3)	
Within 90 days		297 (68.9)	
>90 days and ≤180 days		87 (20.2)	
>180 days and ≤1 year		18 (4.2)	
Immunosuppression		169 (39.2)	
Nursing home resident		121 (28.1)	
Hemodialysis		43 (10.0)	
Bacteremia	78 (37.5)	133 (30.9)	0.094
ICU admission[b]	77 (37.0)	210 (48.7)	0.005
Mechanical ventilation	65 (31.3)	192 (44.5)	0.001

[a] Values are presented as means ± standard deviations.
[b] ICU, intensive care unit.

The distributions of pathogens for CAP and HCAP are provided in Table 2. Methicillin-resistant *Staphylococcus aureus* was the most common pathogen. Patients with HCAP were significantly more likely to be infected with methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, other nonfermenting gram-negative rods, and other *Enterobacteriaceae* than patients with CAP. HCAP patients were significantly less likely to be infected with *Streptococcus pneumoniae*, *Haemophilus* species, and *Legionella pneumophila* serogroup 1 than patients with CAP. For patients classified as having HCAP based on a prior hospitalization, the distributions of bacterial pathogens isolated from the respiratory tracts were similar, favoring nosocomial pathogens regardless of the timing of the previous hospitalization (≤90 days, >90 days and ≤180 days, >180 days and ≤1 year). The community phenotype of methicillin-resistant *Staphylococcus aureus* was not significantly different for methicillin-resistant *Staphylococcus aureus* isolates from patients with CAP than for those with HCAP ([9 of 25] 36% versus [30 of 132] 23%; $P = 0.153$).

Secondary bacteremia occurred in 211 (33.0%) patients. The incidence of secondary bacteremia was not significantly different among patients with CAP than for those with HCAP (37.5% versus 30.9%; $P = 0.094$). The percentages of secondary bacteremia among patients with the various pathogens are provided in Table 2.

Appropriate antimicrobial treatment. Appropriate initial antimicrobial treatment was administered to 490 (76.7%) pa-

TABLE 2. Pathogen distribution

Pathogen	No. (%) of patients with a combination of infections (n = 639)	% of patients with bacteremia	No. (%) of patients with indicated infection		P value
			CAP (n = 208)	HCAP (n = 431)	
MRSA[c]	157 (24.6)	30.6	25 (12.0)	132 (30.6)	<0.001
Streptococcus pneumoniae	130 (20.3)	53.1	85 (40.9)	45 (10.4)	<0.001
Pseudomonas aeruginosa	120 (18.8)	15.8	10 (4.8)	110 (25.5)	<0.001
MSSA[c]	88 (13.8)	23.9	28 (13.5)	60 (13.9)	0.874
Haemophilus species	54 (8.5)	5.6	36 (17.3)	18 (4.2)	<0.001
Other nonfermenting gram-negative rods[a]	46 (7.2)	21.3	4 (1.9)	43 (10.0)	<0.001
Other *Enterobacteriaceae*[b]	44 (6.9)	29.5	5 (2.4)	39 (9.0)	0.002
Klebsiella species	35 (5.5)	34.3	7 (3.4)	28 (6.5)	0.103
Escherichia coli	30 (4.7)	60.0	12 (5.8)	18 (4.2)	0.372
Legionella species	8 (1.3)	0	7 (3.4)	1 (0.2)	0.017

[a] *Acinetobacter* species, *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, *Burkholderia* species.
[b] *Enterobacter* species, *Citrobacter* species, *Serratia marcescens*, *Proteus* species, *Morganella* species.
[c] MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

tients within 24 h of hospital admission, and 149 (23.3%) patients received inappropriate initial antimicrobial treatment. Patients with HCAP were statistically more likely to receive inappropriate antimicrobial treatment than patients with CAP (28.3% versus 13.0%; $P < 0.001$). Figure 1 provides the rates of inappropriate treatment by pathogen distribution. Methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, other nonfermenting gram-negative rods, and other *Enterobacteriaceae* were the most common pathogens to be initially treated with an inappropriate antimicrobial regimen. Of the 220 patients initially treated only with a community-acquired-pneumonia antimicrobial regimen (ceftriaxone plus azithromycin or moxifloxacin), 49 (22.3%) initially received inappropriate antimicrobial treatment (CAP, 15 [13.6%] versus HCAP, 34 [30.9%]; $P = 0.002$).

Hospital mortality rates. The overall hospital mortality rate was 19.6% (125 patients expired during their hospital stays). Patients with HCAP were significantly more likely to die than patients with CAP (24.6% versus 9.1%; $P < 0.001$). Similarly, patients treated with an inappropriate initial antimicrobial regimen had a greater rate of hospital mortality than patients treated with an appropriate initial regimen (32.2% versus 15.7%; $P < 0.001$). Logistic-regression analysis identified seven variables as independent predictors of hospital mortality (Table 3). Administration of inappropriate initial antimicrobial treatment was independently associated with hospital mortality. Figure 2 shows the hospital mortality rate for patients infected with the pathogens associated with culture-positive pneumonia. Methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Esch-*

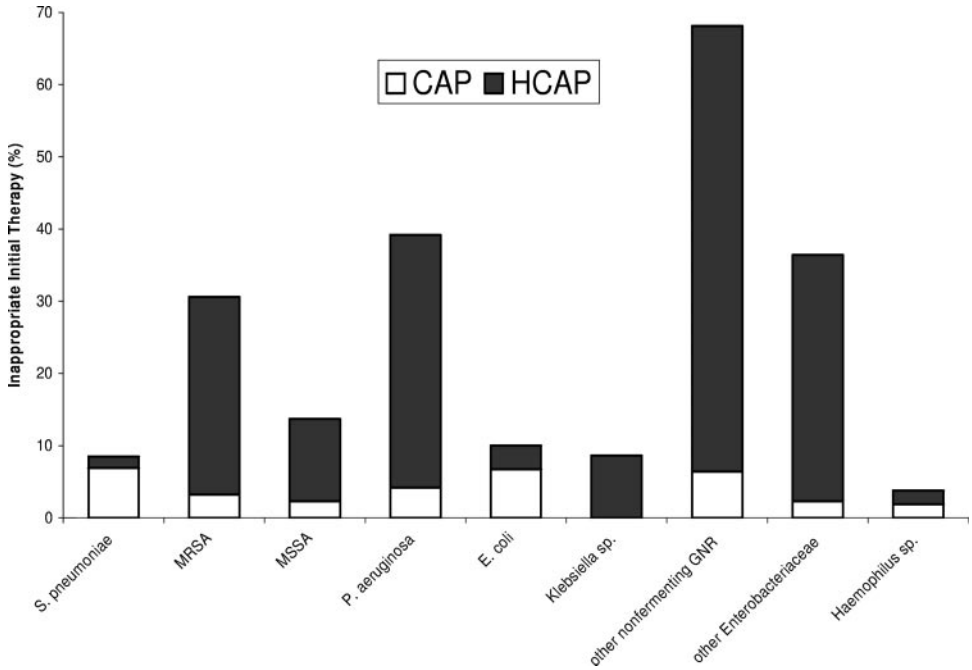

FIG. 1. Rates of inappropriate antimicrobial treatment in patients according to pathogen distribution. GNR, gram-negative rods.

TABLE 3. Multivariate analysis of independent risk factors for hospital mortality[a]

Variable	Adjusted odds ratio	95% CI[b]	*P* value
Age (1-yr increments)	1.02	1.01–1.04	0.001
HCAP	2.28	1.67–3.13	0.009
Requires mechanical ventilation	5.05	3.68–6.92	<0.001
Inappropriate initial antimicrobial therapy	2.19	1.27–3.78	0.005
Bacteremia	3.26	2.54–4.82	<0.001
Caucasian	1.80	1.12–2.89	0.015
Klebsiella species infection	2.53	1.66–3.91	0.034

[a] Other covariates not presented in the table that had a *P* value of >0.05 are intensive care unit admission; monotherapy antibiotic regimen; or infection with methicillin-resistant *Staphylococus aureus*, *Pseudomonas aerginosa*, *Streptococcus pneumoniae*, or methicillin-sensitive *Staphylococcus aureus*. By the Hosmer-Lemeshow goodness-of-fit test, $P = 0.653$.

[b] CI, confidence interval.

erichia coli, *Klebsiella* species, and other nonfermenting gram-negative rods were associated with a hospital mortality rate greater then 20 percent.

DISCUSSION

We showed that in an urban teaching hospital, HCAP was more common than CAP among patients admitted with a culture-positive diagnosis of pneumonia. Methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, methicillin-sensitive *Staphylococcus aureus*, and *Haemophilus influenzae* were the most common pathogens associated with culture-positive pneumonia. HCAP patients were statistically more likely to be infected with methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, other nonfermenting gram-negative rods, and other *Enterobacteriaceae* and were significantly more likely to receive inappropriate initial antimicrobial treatment than patients with CAP. Patients receiving inappropriate initial antimicrobial treatment were significantly more likely to die during their hospitalizations than patients treated with an appropriate initial antimicrobial regimen.

Previous investigations have shown that antimicrobial regimens lacking activity against identified microorganisms causing serious infections (e.g., nosocomial pneumonia, bloodstream infections) are associated with greater rates of hospital mortality (1, 3, 6, 7–11, 13, 15, 17). In these studies, inappropriate initial antimicrobial treatment was most often associated with infection due to potentially antibiotic-resistant bacteria (methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter* species). More recently, a similar finding has been demonstrated for patients with severe sepsis and septic shock (2, 4, 12, 16). Unfortunately, changing antimicrobial therapy to an appropriate regimen for patients with serious nosocomial infections, including pneumonia, after susceptibility data become available has not been demonstrated to improve clinical outcomes in patients initially receiving inappropriate treatment (1, 11, 13). Our present findings are consistent with these previous studies in demonstrating that potentially antibiotic-resistant pathogens (*Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, other nonfermenting gram-negative rods, and other *Enterobactereacae*) were significantly more likely to occur in patients with HCAP and to be treated with an inappropriate antibiotic regimen and that

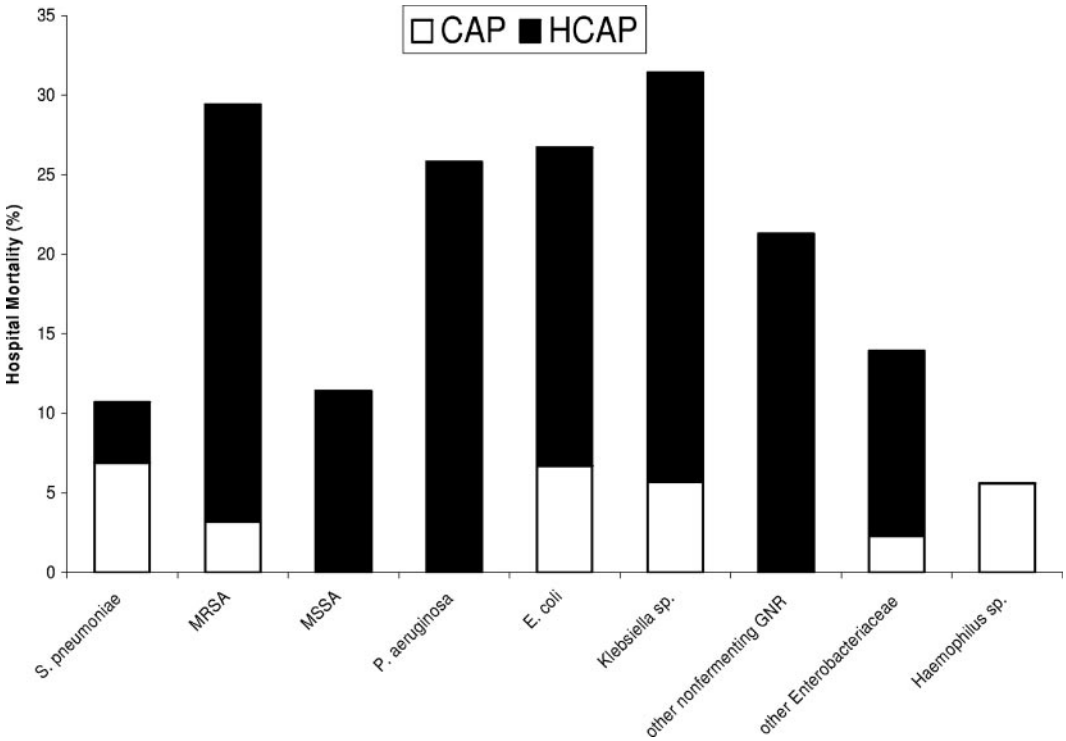

FIG. 2. Rates of hospital mortality according to pathogen distribution. GNR, gram-negative rods.

patients treated with an inappropriate initial antimicrobial regimen were more likely to die during their hospitalizations.

In a previous multicenter study of culture-positive pneumonia from an administrative database, the occurrence of HCAP was found to be less common than CAP (10). Kollef et al. found that among patients with culture-positive pneumonia admitted to the hospital setting, 2,221 (69.2%) had CAP and 988 (30.8%) had HCAP (10). However, the pathogen distribution was similar to our current findings. The multicenter study demonstrated that CAP patients were statistically more likely to be infected with *Streptococcus pneumoniae* (16.6% versus 5.5%; $P < 0.01$) and *Haemophilus influenzae* (16.6% versus 5.8%; $P < 0.01$), whereas patients with HCAP were significantly more likely to be infected with methicillin-resistant *Staphylococcus aureus* (26.5% versus 8.9; $P < 0.01$), *Pseudomonas aeruginosa* (25.3% versus 17.1; $P < 0.01$), or other gram-negative bacteria (9.5% versus 4.1%; $P < 0.01$). The greater frequency of HCAP patients observed at Barnes-Jewish Hospital may be related to the different case mix of patients enrolled in our study. For example, over 90 percent of HCAP patients at Barnes-Jewish Hospital had at least one previous hospitalization during the preceding 12 months, suggesting a high likelihood of exposure to potentially antibiotic-resistant bacteria.

Several important limitations of this investigation should be noted. First, we evaluated only patients with culture-positive pneumonia. Therefore, we may have missed patients with pneumonia having negative cultures due to either early antibiotic administration or inadequate specimens submitted for microbiologic evaluation. Additionally, we did not employ nonculture methods (e.g., serology, PCR assays) to establish the diagnosis of CAP, which limited our ability to identify atypical pathogens (e.g., viruses, *Mycoplasma* species, *Chlamydia* species). This is an important limitation that likely reduced the number of patients with CAP identified. Second, we limited our study to patients with identified bacterial pneumonia, excluding all other causes. Therefore, our findings are not applicable to patients with nonbacterial causes of pneumonia. Third, we did not employ a severity-of-illness score. It is possible that the patients who died after inappropriate initial antimicrobial treatment may have been sicker than those who received appropriate initial treatment. The results of our multivariate analysis refute this in showing that markers of greater disease severity (older age, requiring mechanical ventilation) were independently associated with mortality along with the administration of inappropriate initial antimicrobial treatment. Lastly, our study was performed at a single hospital and may not be applicable to other hospitals. For example, hospitals caring for patients who infrequently have risk factors for HCAP would not expect to see similar rates of inappropriate initial antimicrobial treatment among patients with culture-positive pneumonia admitted to their hospitals.

The observed impact of inappropriate initial antimicrobial therapy on patient outcomes suggests that measures aimed at improving the administration of appropriate antibiotic therapy to patients with risk factors for HCAP is required. Micek et al. previously demonstrated in the emergency department setting that a standardized order set for the treatment of severe sepsis and septic shock increased the administration of appropriate initial antimicrobial therapy from 71.7% to 86.7% and was associated with a significant reduction in hospital mortality (16). The standardized order set required physicians to screen patients for health care-associated infection risk factors and to treat with a combination antimicrobial regimen targeting methicillin-resistant *Staphylococcus aureus* and potentially resistant gram-negative bacteria when these risk factors were identified. A similar study by Ibrahim et al. found that a treatment protocol for the management of ventilator-associated pneumonia increased the administration of initial appropriate antimicrobial therapy employing a combination antimicrobial regimen (7). Implementation of standardized approaches for the treatment of HCAP and other health care-associated infections seems reasonable, since failure to identify risk factors for health care-associated infections appears to be the most common cause for the administration of inappropriate antimicrobial therapy to patients hospitalized with serious infections (16, 18).

In summary, we found that HCAP was more common than CAP among patients with culture-positive pneumonia admitted to an urban teaching hospital. Patients with HCAP were more likely to receive inappropriate initial antimicrobial treatment and had a greater risk of hospital mortality. Clinicians caring for patients with pneumonia requiring hospital admission should be aware of the risk factors for HCAP and the predominant bacterial pathogens associated with health care-associated infections at their hospitals. Awareness of these issues may result in improved rates of initial administration of appropriate antimicrobial treatment to patients with HCAP. Additionally, new studies are required to develop uniform and validated criteria for HCAP and other health care-associated infections.

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