

# Improving Outcomes in Elderly Patients With Community-Acquired Pneumonia by Adhering to National Guidelines

## Community-Acquired Pneumonia Organization International Cohort Study Results

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**Background:** To define whether elderly patients hospitalized with community-acquired pneumonia (CAP) had better outcomes if they were treated with empirical antimicrobial therapy adherent to the 2007 Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines for CAP.

**Methods:** This was a secondary analysis of the CAPO International Cohort Study database, which contained data from a total of 1725 patients aged 65 years or older who were hospitalized with CAP. Data from June 1, 2001, until January 1, 2007, were analyzed from 43 centers in 12 countries including North America (n=2), South America (n=4), Europe (n=4), Africa (n=1), and Southeast Asia (n=1). Initial empirical therapy for CAP was evaluated for guideline compliance according to the 2007 IDSA/ATS guidelines for CAP. Time to clinical stability, length of stay (LOS), total in-hospital mortality, and CAP-related mortality for each group were calculated. Comparisons between groups were made using cumulative incidence curves and competing risks regression.

**Results:** Among the 1649 patients with CAP, aged 65

years or older, 975 patients were given antimicrobial regimens adherent to the IDSA/ATS for CAP guidelines, while 660 patients were treated with nonadherent regimens (465 patients were “undertreated”; 195 were “overtreated”). Adherence to guidelines was associated with a statistically significant decreased time to achieve clinical stability compared with nonadherence: the proportion of patients who reached clinical stability by 7 days was 71% (95% confidence interval [CI], 68%-74%) and 57% (95% CI, 53%-61%) ( $P < .01$ ), respectively. Guideline adherence was also associated with shorter LOS (median adherence LOS, 8 days; interquartile range [IQR], 5-15 days; median nonadherence LOS, 10 days; IQR, 6-24 days) ( $P < .01$ ) and decreased overall in-hospital mortality (8%; 95% CI, 7%-10% vs 17%; 95% CI, 14%-20%) ( $P < .01$ ).

**Conclusion:** Implementation of national guidelines at the local hospital level will improve not only mortality and LOS of elderly patients hospitalized with CAP but also time to clinical stability.

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**C**OMMUNITY ACQUIRED pneumonia (CAP) causes significant morbidity and mortality worldwide in elderly patients.<sup>1</sup> Death due to pneumonia has been reported as high as 20% in this population.<sup>2</sup> Most patients hospitalized for CAP are elderly ( $\geq 65$  years), and the annual cost of treatment is \$4.8 billion, compared with \$3.6 billion for patients younger than 65 years.<sup>3</sup>

See also pages 1462 and 1525

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Furthermore, the demographics, risk factors, clinical presentation, and disease etiology in elderly patients with CAP are different than those in younger popula-

tions. Elderly patients may present with few classic respiratory signs and symptoms but rather have delirium, worsening of chronic confusion, and falls.<sup>4,5</sup> There is also a high incidence of silent aspiration in elderly patients with CAP.<sup>6</sup> The most commonly identified pathogen causing CAP in nursing home patients has lately been *Streptococcus pneumoniae*,<sup>7</sup> but a later study found *Staphylococcus aureus* to fill that role.<sup>8</sup> Most studies reporting atypical pathogens found a lower incidence in older populations.<sup>7,9</sup> Overall, elderly patients have a unique clinical presentation of CAP with risk factors that are distinct from those of younger patients.

The Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines<sup>10</sup> recommend initi-

**Table 1. 2007 IDSA/ATS Guideline Recommendations<sup>10</sup> for Empirical Therapy for Community-Acquired Pneumonia**

Inpatients, non-ICU treatment
A respiratory fluoroquinolone
A $\beta$ -lactam plus a macrolide
Inpatients, ICU treatment
A $\beta$ -lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin <sup>a</sup> or a respiratory fluoroquinolone <sup>b</sup>
<b>Special Concerns</b>
If <i>Pseudomonas</i> is a concern:
A $\beta$ -lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin
or
The above $\beta$ -lactam plus an aminoglycoside and azithromycin <sup>c</sup>
or
The above $\beta$ -lactam plus an aminoglycoside and a fluoroquinolone <sup>b</sup>
If community-acquired MRSA is a concern:
Add vancomycin or linezolid

Abbreviations: ICU, intensive care unit; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; MRSA, methicillin-resistant *Staphylococcus aureus*.

<sup>a</sup>Because the guidelines say that "overall efficacy remains good for many classes of agents,"<sup>10(pS44)</sup> clarithromycin was considered adherent as well.

<sup>b</sup>Gatifloxacin, levofloxacin, or moxifloxacin.

<sup>c</sup>Substitute "the above  $\beta$ -lactam" with aztreonam for penicillin-allergic patients.

ating empirical antimicrobial therapy for all hospitalized patients with a regimen that covers the most common typical as well as atypical pathogens. The guidelines cite several studies that include a substantial proportion of elderly patients,<sup>7,11,12</sup> but to our knowledge, no study has evaluated the impact of the new pneumonia guidelines exclusively on the elderly population.

Literature regarding CAP in the elderly population has focused on defining prognostic factors, etiology, and prevention, but not on whether outcomes are improved if the guidelines for CAP are adhered to. The primary objective of this study was to determine whether elderly patients with CAP had better outcomes, including time to clinical stability, if they were treated with empirical antimicrobial therapy adherent to the 2007 IDSA/ATS guidelines<sup>10</sup> for CAP. Secondary objectives were to define the outcomes among patients who received a  $\beta$ -lactam alone and among patients who were infected with pathogens typically causing health care-associated pneumonia (HCAP).

## METHODS

### POPULATION AND STUDY DESIGN

The CAPO International Cohort Study<sup>13</sup> is an international, observational, retrospective study of hospitalized patients with CAP. A secondary analysis was performed of the CAPO study database. Data from June 1, 2001, until January 1, 2007, were collected from hospitalized patients 65 years or older from 43 hospitals in 12 countries. In each participating center, primary investigators randomly selected 1 or more patients from a list of hospitalized patients with a diagnosis of CAP. Data were collected on a case report form, entered into a computer, and transferred electronically to the CAPO coordinating center at the University of Louisville ([www.caposite.com](http://www.caposite.com)). Each local internal review board approved the study, and patient consent was waived due to the retrospective and observational study de-

sign. A group of investigators at the University of Louisville validated the quality of data by checking for discrepancies and inconsistencies, which, when found, were communicated to the respective primary investigator to correct or clarify before the cases were entered into the database.

### DEFINITION OF CAP

Pneumonia was defined as the presence of a new pulmonary infiltrate found on chest radiograph plus a new or increased cough, abnormal temperature ( $<35.6^{\circ}\text{C}$  or  $>37.8^{\circ}\text{C}$ ), or abnormal leukocyte count (leukocytosis, left shift, or leukopenia as defined by local laboratory values). Pneumonia was not considered in patients with a chronic infiltrate similar to that seen on previous chest radiographs. Pneumonia was considered hospital acquired in patients previously hospitalized who were discharged less than 14 days prior to evaluation. Pneumonia was diagnosed on the day of admission, which was defined as day zero. The cause of CAP was declared if 1 of the following conditions was met: (1) positive findings for a bacterial pathogen in blood cultures; or (2) positive findings from endotracheal aspirate, bronchoscopy sample (protected brush or lavage), pleural fluid, or sputum cultures. Sputum cultures were restricted to sputum samples according to respective local hospital microbiology laboratory policy (eg, specimens must not be saliva or have  $>25$  squamous epithelial cells).

### ADHERENCE WITH IDSA/ATS GUIDELINES

Empirical therapy within the first 24 hours of hospitalization was evaluated for adherence or nonadherence to the 2007 IDSA/ATS guidelines for CAP (**Table 1**).<sup>10</sup> Adherence to the guidelines was defined as empirical antimicrobial therapy consistent with recommendations in the guidelines. Ciprofloxacin was not considered a "respiratory fluoroquinolone" and was evaluated for adherence or nonadherence only in the context of antipseudomonal coverage. The 2007 IDSA/ATS guidelines for CAP allow coverage for *Pseudomonas aeruginosa* or methicillin-resistant *S aureus* (MRSA) if risk factors for those specific pathogens are present. Because we did not know the multidrug-resistant risk factor status, a patient's initial therapy was considered adherent if it included coverage for *P aeruginosa* or MRSA, as outlined in Table 1 (eg, levofloxacin plus vancomycin). Nonadherence was defined as empirical coverage that was either narrower than the one described in the guidelines (eg, ceftriaxone alone) or broader (ceftriaxone plus azithromycin plus moxifloxacin). If a patient was treated with, for example, an antipseudomonal  $\beta$ -lactam plus a macrolide, then the regimen was considered nonadherent because the guidelines recommend a more narrow regimen for a patient with CAP or double antipseudomonal coverage if risk factors for *P aeruginosa* are present. Undertreatment was defined as a nonadherent regimen that covered less than what is recommended in the guidelines, while overtreatment was defined as a regimen that covered more than what is recommended.

### STUDY OUTCOMES

Time to clinical stability was defined in days and calculated as the day that the patient met the criteria for switch from intravenous to oral therapy minus the day of admission. The ATS criteria<sup>14</sup> for switch to oral therapy were used, which include improving symptoms (cough and dyspnea), no fever for at least 8 hours (temperature  $<37.7^{\circ}\text{C}$  [ $<100^{\circ}\text{F}$ ]), decreasing white blood cell count, and adequate oral intake. Time to clinical stability was censored at day 7 if criteria were not met by then. Total length of stay (LOS) was defined in days and calculated

**Table 2. Severity of Disease and Demographics Among Patients Treated With Adherence and Nonadherence to the 2007 IDSA/ATS Guidelines<sup>10</sup> for Community-Acquired Pneumonia<sup>a</sup>**

Characteristic	Guideline-Adherent Treatment (n = 975)	Guideline-Nonadherent Treatment		P Value
		Undertreatment (n = 465)	Overtreatment (n = 195)	
Male	602 (62)	254 (55)	126 (65)	.01
Age, mean, y	78.8	80.0	78.0	<.01
Nursing home residence	65 (7)	49 (11)	30 (15)	<.01
PSI, median	105	111	117	<.01
Risk class				
I-III	264 (27)	96 (21)	36 (18)	<.01
IV-V	711 (73)	369 (79)	159 (82)	
I	0	1 (<1)	0	
II	45 (5)	11 (2)	11 (6)	NR
III	219 (22)	84 (18)	25 (13)	NR
IV	505 (52)	224 (48)	94 (48)	NR
V	206 (21)	145 (31)	65 (33)	NR
Comorbidities				NR
COPD	361 (37)	141 (30)	75 (38)	.03
CHF	276 (28)	139 (30)	51 (26)	.61
Stroke	197 (20)	149 (32)	36 (18)	<.01
Renal disease	139 (14)	65 (14)	30 (15)	.89
Liver disease	28 (3)	12 (3)	6 (3)	.93
Diabetes mellitus	222 (23)	89 (19)	51 (26)	.11
Cancer	94 (10)	67 (14)	28 (14)	.01

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; PSI, pneumonia severity index.

<sup>a</sup>Unless otherwise indicated, data are reported as number (percentage) of patients.

as the day of discharge minus the day of admission. The LOS was censored at 30 days in an effort to identify patients whose LOS was CAP related (LOS ≤30 days). In-hospital all-cause mortality was assessed for all patients at discharge or on day 28 if the patient was still hospitalized. All CAP-related mortality was determined clinically by a patient's principal investigator. Pathogens considered to be associated with HCAP were *Acinetobacter*, *Enterobacter*, *Proteus*, *Pseudomonas*, and *Serratia* species, *Klebsiella pneumoniae*, and MRSA.

### STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software, version 16.1 (SPSS Inc, Chicago, Illinois), and R, version 2.8.1.<sup>15</sup> Clinical and demographic characteristics of each patient group based on antimicrobial guideline adherence or nonadherence were computed and compared using parametric and nonparametric statistics, where appropriate. Disease severity was defined by the pneumonia severity index (PSI).<sup>16</sup> Univariate time to event analysis, including the generation and comparison of cumulative incidence curves,<sup>17</sup> was performed to assess the impact of guideline adherence on time to clinical stability and LOS. To properly account for patients who died in the hospital, in-hospital mortality was treated as a competing risk in the analysis. The proportions of patients who reached clinical stability by day 7 and were discharged by day 14 were calculated for each group. All-cause mortality was also assessed using competing risks analysis, with patients who were discharged no longer considered to be at risk of dying in the hospital. For CAP-related mortality, death from other causes was also considered a competing risk. Cumulative incidence curves were compared using the  $\chi^2$  test statistics outlined by Gray.<sup>18</sup>

The primary factor of interest in the multivariable analysis was the type of antimicrobial therapy (guideline adherent or nonadherent). The proportional hazards regression model for competing risks was used to assess factors affecting time to clinical

stability and LOS.<sup>19</sup> Other variables included in the models were disease severity and processes of care. *Disease severity* included high-risk class (PSI, IV or V), intensive care unit (ICU) admission, multilobar pneumonia, pleural effusion, altered mental status, tachypnea (respiratory rate, >30 breaths/min), and hypotension (systolic blood pressure, <90 mm Hg). *Processes of care* included receiving antimicrobials within 8 hours of admission, a pneumococcal vaccine, blood cultures within 24 hours of admission, and oxygen assessment. Multivariable models were evaluated for possible interactions between covariates and interactions between covariates and time (time-dependent effects). All patients who were missing information on antibiotic timing (n=167) were removed from the regression models. No other covariates had missing information.

### RESULTS

Among 1649 elderly patients included, 975 had initial antimicrobial therapy adherent to the guidelines for CAP, while 660 patients had initial antimicrobial therapy nonadherent to the guidelines. The demographics of all patients and severity of disease with respect to guideline adherence and nonadherence (overtreated and undertreated) are outlined in **Table 2**. Patients receiving nonadherent treatment had a higher median PSI, although the mean of all groups was in risk class IV. A greater proportion of patients receiving nonadherent treatment were nursing home residents or those who had cerebrovascular disease or cancer. Among undertreated patients, more were women, and a slightly smaller proportion had chronic obstructive pulmonary disease relative to overtreated patients and those receiving adherent treatment. **Table 3** lists the organisms isolated in the 20% of the

**Table 3. The Incidence of Isolated Pathogens Among Patients Who Had a Pathogen Identified<sup>a</sup>**

Pathogen <sup>b</sup>	CAP Treatment <sup>c</sup>		P Value
	Adherent	Nonadherent	
<i>Streptococcus pneumoniae</i>	80 (14)	41 (12)	.07
<i>Staphylococcus aureus</i>	29 (9)	36 (11)	.10
MRSA	14 (4)	16 (5)	.34
<i>Haemophilus influenzae</i>	26 (8)	18 (5)	.75
<i>Moraxella catarrhalis</i>	18 (5)	8 (2)	.22
<i>Legionella</i> species	6 (2)	8 (2)	.41
<i>Chlamydia pneumoniae</i>	3 (1)	3 (1)	>.99
<i>Mycoplasma pneumoniae</i>	2 (1)	3 (1)	.66
<i>Pseudomonas aeruginosa</i>	14 (4)	15 (4)	.44
<i>Escherichia coli</i>	5 (1)	10 (3)	.11
<i>Klebsiella pneumoniae</i>	6 (2)	4 (1)	>.99
<i>Enterobacter</i> species	2 (1)	4 (1)	.41
<i>Proteus</i> species	1 (<1)	2 (1)	.59
<i>Acinetobacter</i> species	2 (1)	1 (1)	>.99
Other <sup>d</sup>	6 (2)	7 (2)	.57
Total	186 (56)	146 (44)	NA

Abbreviations: CAP, community-acquired pneumonia; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable.

<sup>a</sup>Unless otherwise indicated, data are reported as number (percentage) of patients; 332 of the 1635 study patients had a pathogen identified (20%).

<sup>b</sup>Thirty-seven patients had combined infections of 2 pathogens.

<sup>c</sup>Adherent and nonadherent describe the treatment regimens with regard to the 2007 IDSA/ATS guidelines.<sup>10</sup>

<sup>d</sup>"Other" includes *Enterococcus fecalis*, mixed anaerobic bacteria, *Salmonella* species, *Serratia* species, and *Streptococcus pyogenes*.

population who had an organism identified. *Streptococcus pneumoniae* was the most common organism found among patients in both groups, followed by *S aureus*. **Table 4** lists the proportions of each antimicrobial regimen used. Nearly all patients receiving adherent treatment received either a  $\beta$ -lactam plus a macrolide (59%) or a quinolone (40%) as empirical treatment. The predominant nonadherent regimen was  $\beta$ -lactam alone (52%). The predominant regimens for patients who had HCAP pathogens were a  $\beta$ -lactam plus a macrolide (35%), a quinolone (13%), and a  $\beta$ -lactam alone (25%).

Univariate and multivariable analyses for time to clinical stability favored patients given adherent therapy. The estimated probability of reaching clinical stability within 7 days was 0.71 (95% confidence interval [CI], 0.68-0.74) for those who received guideline-adherent therapy (n=995), and 0.57 (95% CI, 0.53-0.61) for those who received guideline nonadherent therapy (n=660). Comparison of cumulative incidence curves showed significant differences between the adherent, undertreated, and overtreated groups, with patients treated in adherence to the guidelines having a higher estimated probability of reaching clinical stability by any given day ( $P < .01$ ) (**Figure 1A**). Based on multivariable competing risks regression, the rate at which patients reached clinical stability was significantly higher for those receiving adherent treatment, with a hazard ratio (HR) of 1.44 ( $P < .01$ ) for adherence vs undertreatment and 1.33 ( $P < .01$ ) for adherence vs overtreatment. That is, patients receiving adherent treatment reached clinical stability at a rate 1.44 and 1.33 times faster than undertreated and overtreated

**Table 4. The Number and Proportion of IDSA/ATS Guideline-Adherent<sup>10</sup> vs Nonadherent Empirical Antimicrobial Regimens Used for Hospitalized Patients With CAP**

Antimicrobial Regimen	Patients, No. (%)
<b>Adherent</b>	
$\beta$ -Lactam <sup>a</sup> + macrolide	571 (58.6)
$\beta$ -Lactam <sup>a</sup> + macrolide + vancomycin <sup>b</sup>	1 (<1)
Quinolone	387 (39.7)
Quinolone + vancomycin <sup>b</sup>	2 (<1)
Quinolone <sup>c</sup> + $\beta$ -lactam <sup>a</sup>	12 (1.2)
Quinolone <sup>c</sup> + $\beta$ -lactam <sup>a</sup> + vancomycin <sup>b</sup>	2 (<1)
<b>Nonadherent</b>	
$\beta$ -Lactam <sup>a</sup>	343 (52.0)
$\beta$ -Lactam <sup>a</sup> + other <sup>d</sup>	65 (9.8)
$\beta$ -Lactam (antipseudomonal) <sup>a</sup> + macrolide	21 (3.2)
$\beta$ -Lactam <sup>a</sup> + macrolide + quinolone or other <sup>d</sup>	66 (10.0)
Quinolone + macrolide	8 (1.2)
Quinolone + $\beta$ -lactam <sup>a</sup> ± other <sup>d</sup>	69 (10.5)
Quinolone + other <sup>d</sup>	27 (4.1)
Macrolide ± other <sup>d</sup>	19 (2.9)
Other <sup>d</sup>	27 (4.1)

Abbreviations: CAP, community-acquired pneumonia; IDSA/ATS, Infectious Diseases Society of America/American Thoracic Society; MRSA, methicillin-resistant *Staphylococcus aureus*.

<sup>a</sup>The 2007 IDSA/ATS guidelines<sup>10</sup> do not recommend using an antipseudomonal  $\beta$ -lactam unless risk factors for *Pseudomonas aeruginosa* are present. Use of 1 agent implies a desire to cover for *P aeruginosa*, but regimens with an antipseudomonal  $\beta$ -lactam were considered adherent only if used with another antipseudomonal agent.

<sup>b</sup>The IDSA/ATS guidelines<sup>10</sup> for CAP treatment require risk factors for methicillin-resistant *Staphylococcus aureus* be present to justify the use of vancomycin.

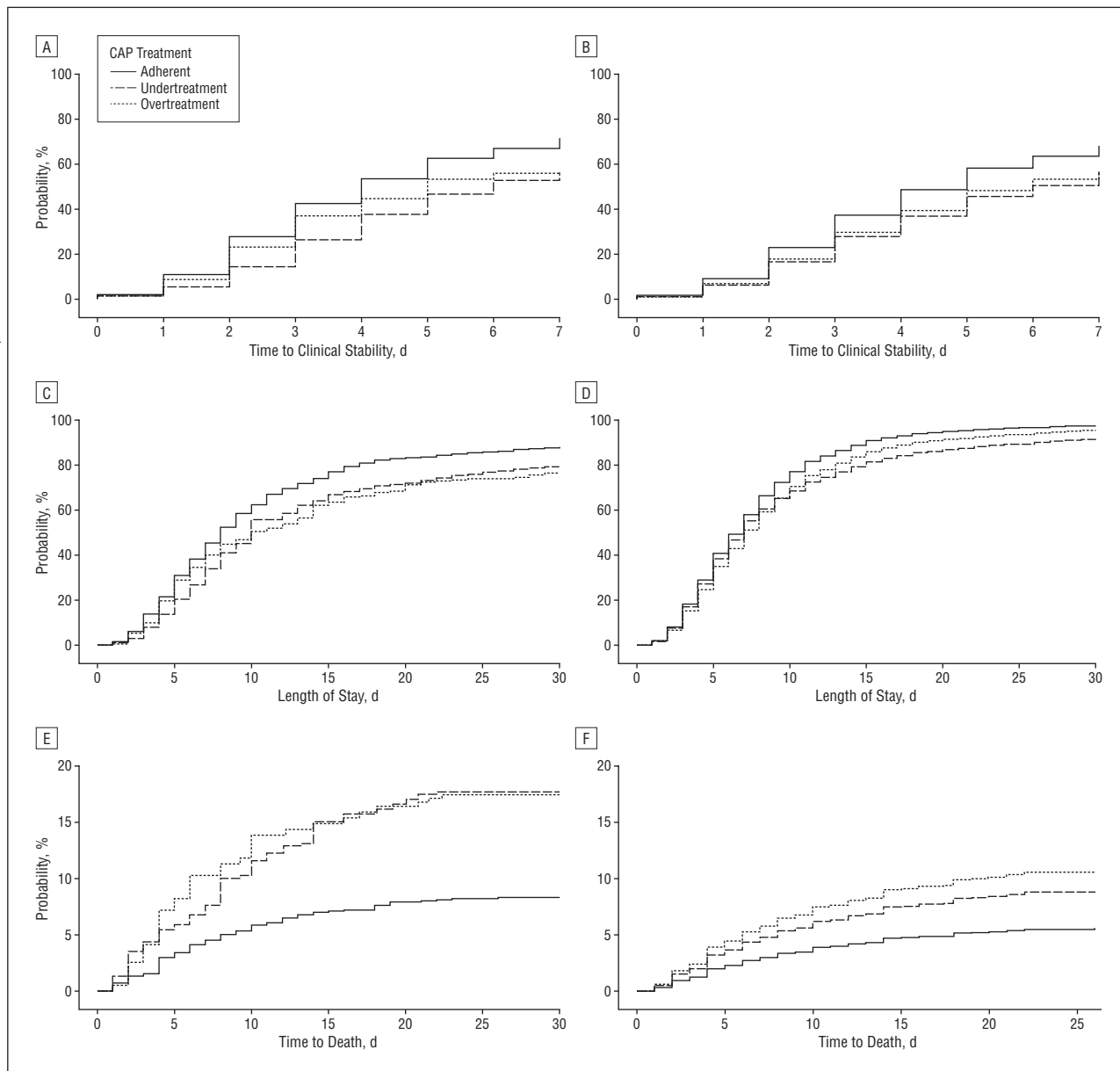
<sup>c</sup>This regimen is considered adherent only for patients admitted to an intensive care unit.

<sup>d</sup>"Other" indicates that 1 or more antimicrobials from the following list were used: aztreonam, chloramphenicol, ciprofloxacin, clindamycin, gentamicin, metronidazole, penicillin G, rifampin, trimethoprim/sulfamethoxazole, and/or tobramycin.

patients, respectively (**Figure 2**). Adjusted incidence curves for the 3 groups, based on the multivariable regression model, are shown in Figure 1B (mean values were used for the other covariates). Other variables showing significance for patients more likely to reach clinical stability within 1 week were antibiotics given within 8 hours and pneumococcal vaccine. Variables found less likely to be associated with patients reaching clinical stability within 1 week were high risk class, ICU admission, the presence of multilobar pneumonia, altered mental status, and tachypnea.

The median LOS for those who received guideline-adherent therapy (n=975) was 8 days, with an interquartile range (IQR) of 5 to 15 days, and the median LOS for those who received guideline nonadherent therapy (n=660) was 10 days (IQR, 10-4 days). Univariate analysis comparing cumulative incidence curves to 30 days between the adherent, undertreated, and overtreated groups showed significant differences, with patients treated in adherence to the guidelines leaving the hospital more quickly than the nonadherent group ( $P = .01$ ) (**Figure 1C**). Adjusted incidence curves for the 3 groups, based on the multivariable regression model, are shown in Figure 1D. The rate of hospital discharge for patients treated in adherence to the guidelines was significantly higher than



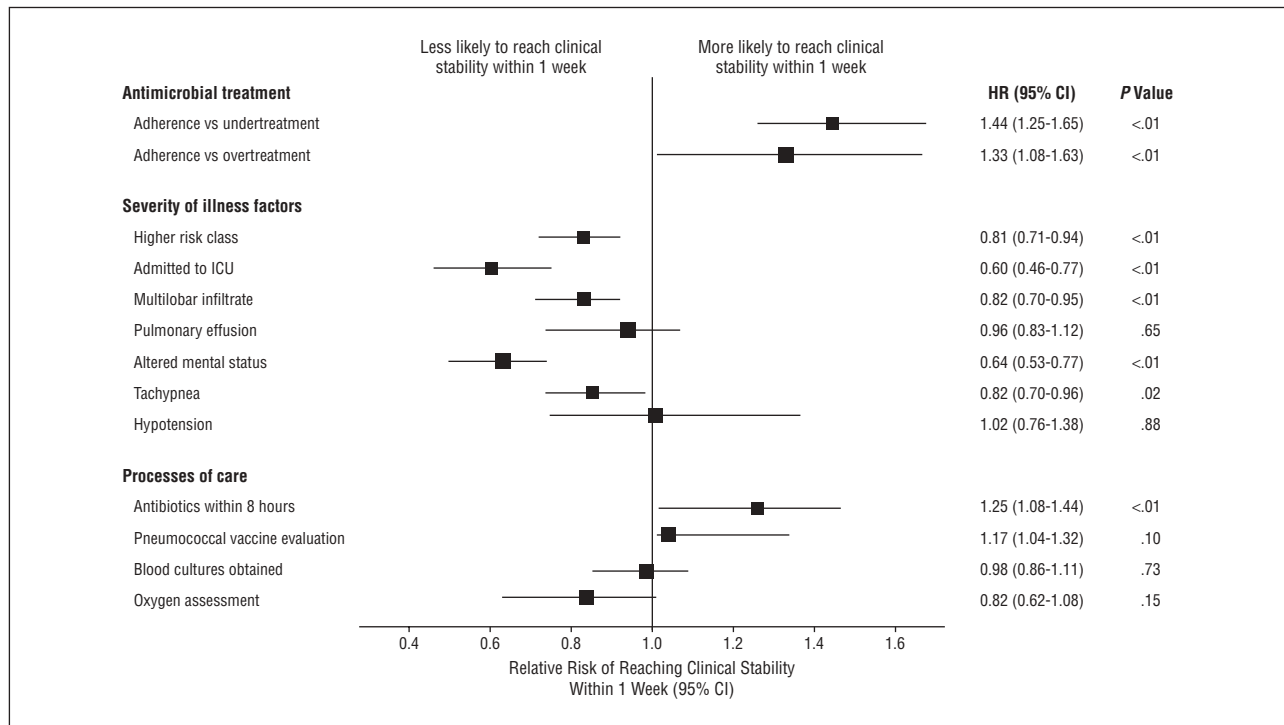


**Figure 1.** Cumulative incidence curves. A and B, Time to clinical stability; C and D, length of stay; and E and F, total mortality for elderly patients with community-acquired pneumonia (CAP). A, C, and E, unadjusted curves. B, D, and F, Adjusted curves based on predictions from the competing risks proportional hazards model (based on mean values of all other covariates). *Adherent* is defined as an antimicrobial treatment regimen that followed the Infectious Diseases Society of America/American Thoracic Society guidelines<sup>10</sup> for the treatment of CAP.

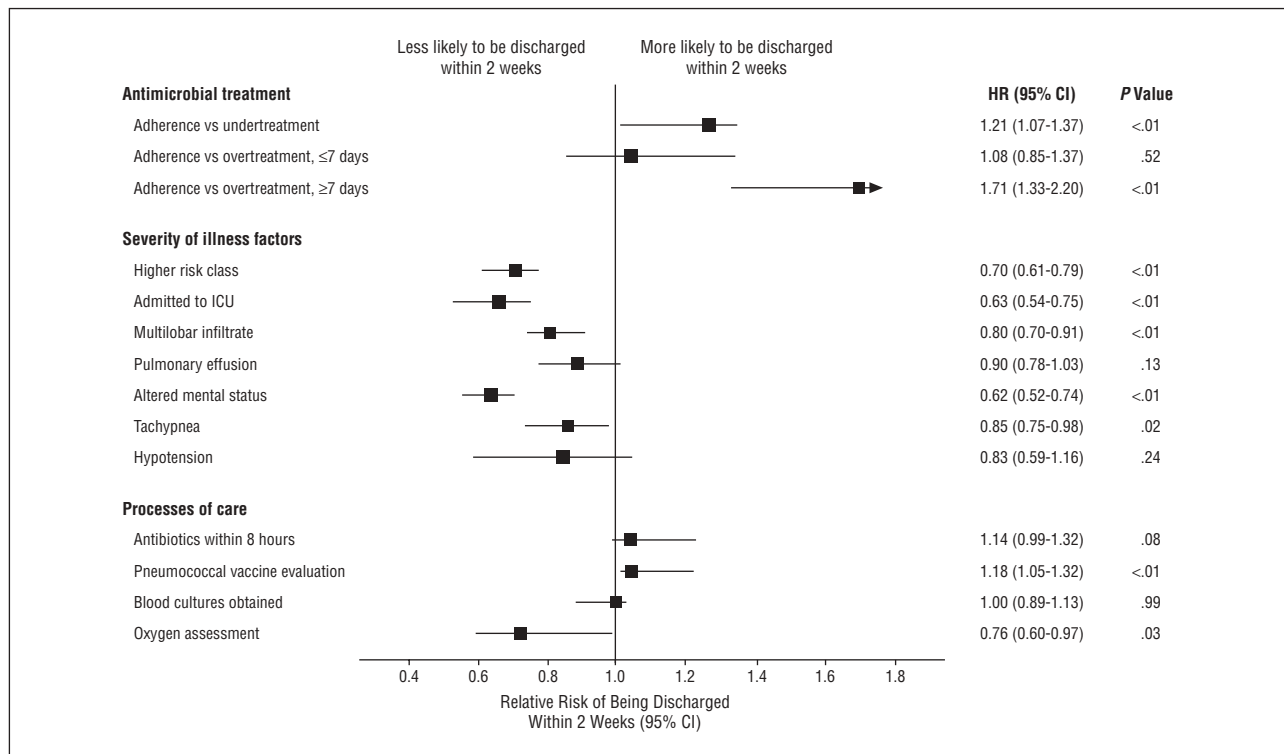
for undertreated patients in multivariable analysis (HR, 1.21) ( $P < .01$ ). For comparisons with overtreated patients, we added a time-dependent effect, since the discharge rate ratio between overtreated patients and those treated in adherence to the guidelines appears to change around day 7. The rate of discharge for adherently treated patients vs overtreated patients was not significant for stays of a week or less (HR, 1.08) ( $P = .52$ ), but for stays longer than a week, the overtreated patients left the hospital at a significantly decreased rate (HR 1.71) ( $P < .01$ ). Another variable showing significant association with earlier hospital discharge was pneumococcal vaccination (HR, 1.15) ( $P < .01$ ). Variables showing significance for patients less likely to be discharged within 30 days were high risk class, admission to an ICU, the presence of mul-

tilobar pneumonia, pleural effusion, altered mental status, and tachypnea (**Figure 3**).

Patients who received adherent therapy died less often than patients who did not. A total of 82 patients among 975 died after receiving adherent therapy (8.4%) vs 121 of 660 patients who died after nonadherent therapy (18.3%). Comparison of cumulative incidence curves showed significant differences between adherence on the one hand and overtreatment or undertreatment on the other (Figure 1E) ( $P < .01$ ). Multivariable analysis also showed a significantly decreased rate of in-hospital mortality for patients treated in adherence to the guidelines relative to undertreated (HR, 0.62) ( $P < .01$ ) and overtreated patients (HR, 0.51) ( $P < .01$ ) (**Figure 4**). Adjusted mortality incidence curves based on the regres-



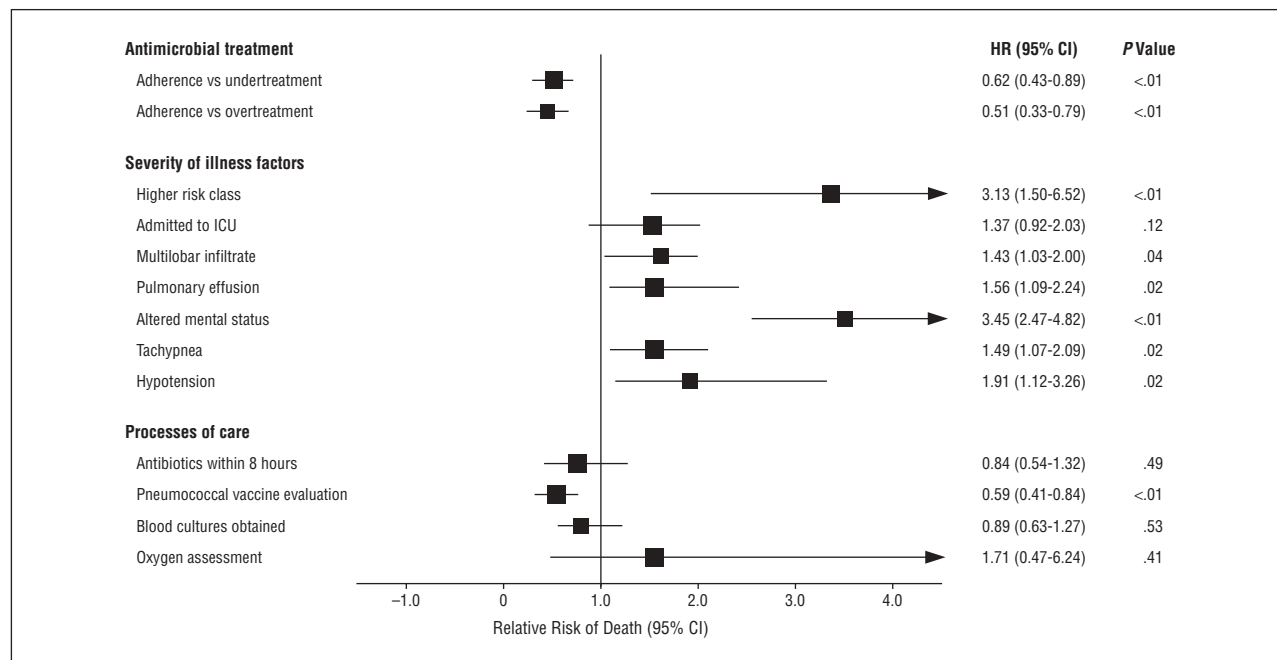
**Figure 2.** Forest plot of the hazard ratios (HRs) (95% confidence intervals [CIs]) for time to clinical stability among elderly patients with community-acquired pneumonia (CAP). The primary variable analyzed was adherence or nonadherence (overtreatment or undertreatment) to an antimicrobial treatment regimen that followed the Infectious Diseases Society of America/American Thoracic Society guidelines<sup>10</sup> for the treatment of CAP. ICU indicates intensive care unit.



**Figure 3.** Forest plot of the hazard ratios (HRs) (95% confidence intervals [CIs]) for length of stay among elderly patients with community-acquired pneumonia (CAP). The primary variable analyzed was adherence or nonadherence (overtreatment or undertreatment) to an antimicrobial treatment regimen that followed the Infectious Diseases Society of America/American Thoracic Society guidelines<sup>10</sup> for the treatment of CAP. ICU indicates intensive care unit.

sion model are shown in Figure 1F. The spread between the adjusted curves in Figure 1F is smaller than that seen in Figure 1E because the patients treated in nonadher-

ence to the guidelines tended to have higher levels of other risk factors for mortality. Cumulative incidence curves were markedly different between adherence, undertreat-



**Figure 4.** Forest plot of the hazard ratios (HRs) (95% confidence intervals [CIs]) for total mortality among elderly patients with community-acquired pneumonia (CAP). The primary variable analyzed was adherence or nonadherence (overtreatment or undertreatment) to an antimicrobial treatment regimen that followed the Infectious Diseases Society of America/American Thoracic Society guidelines<sup>10</sup> for the treatment of CAP. ICU indicates intensive care unit.

ment, and overtreatment ( $P < .01$ ), while the findings of multivariable analysis were significant over a smaller curve spread (HR, 0.61 for adherence vs undertreatment [ $P = .05$ ] and HR, 0.52 for adherence vs overtreatment [ $P = .04$ ]). Patients treated in adherence to the guidelines also had reduced incidence of CAP-related mortality (41 of 975 in the adherence group [4.2%] vs 65 of 660 in the nonadherence group [9.9%]) ( $P < .01$ ).

A subanalysis was performed of patients who received  $\beta$ -lactam only (343 patients, or 52% of the patients treated nonadherently). Patients receiving  $\beta$ -lactam alone were less likely to reach clinical stability by day 7 (59% vs 71%) ( $P < .01$ ), had a higher median LOS (8 vs 10 days) ( $P < .01$ ), and had higher total mortality (17% vs 8%) ( $P < .01$ ). An additional subanalysis was performed on those patients having HCAP. Among 69 patients, 34 received guideline-adherent therapy (49%), while 28 were undertreated (41%), and 7 were overtreated (10%). The estimated probability to reach clinical stability by day 7 was higher in the group treated in adherence to the guidelines than in the patients treated in nonadherence to the guidelines (62% vs 34%) ( $P = .02$ ); the median LOS was lower (11 vs 23 days) ( $P = .04$ ); and the total mortality was lower (15% vs 34%) ( $P = .05$ ).

#### COMMENT

To our knowledge, this study shows for the first time in an exclusively elderly population that time to clinical stability, LOS, and mortality were improved with adherence to the 2007 IDSA/ATS guidelines for CAP.<sup>10</sup> Our findings emphasize that implementation and adherence to guidelines are critical for improved patient care. Guideline adherence may be improved with comprehensive hospital programs created for this purpose.<sup>20,21</sup> However, edu-

cational programs that are mainly didactic and without feedback have not been effective.<sup>22</sup> Guideline implementation at the local hospital level using multidisciplinary programs, especially those providing feedback, will become more important as the incidence of elderly patients with CAP increases.

Despite adjustments for severity of illness and comorbidities, the improved outcomes associated with guideline adherence found in this study may be owing to a higher proportion of patients with either factor in the guideline nonadherence group. However, the amount of increased severity and additional comorbidities were not as great as the proportion of patients in the nonadherence group who received a  $\beta$ -lactam-based regimen without coverage for atypical pathogens (66%). Experiencing worse outcomes due to increased comorbidities is well established,<sup>23</sup> while causing worse outcomes by not using a guideline-adherent regimen in the elderly should be better appreciated.

Another cause for the difference in outcomes between the populations in the present study might be the immunomodulatory effects of macrolides, the universal treatment for atypical pathogens such as *Legionella pneumophila*.<sup>10,24,25</sup> Our group recently showed, in a study using extensive laboratory testing for atypical pathogens and separate secondary analysis of the CAPO database, that outcomes improved in patients treated for CAP who received coverage for atypical pathogens vs those who did not.<sup>25</sup> Among 4337 patients with CAP from 21 countries, 22% tested positive for atypical pathogens. In general, atypical pathogens have been reported to cause approximately 20% of CAP and are known to cause up to 38% of CAP in hospitalized patients.<sup>26</sup> A study of elderly patients, however, found that regimens that included coverage for atypical pathogens were associated

with a lower mortality rate.<sup>11</sup> The incidence of atypical pneumonia in elderly patients was reported to be similar to that in younger patients,<sup>27</sup> although less so in 305 very elderly patients (>80 years of age) compared with 1169 patients younger than 80 years (<1.0% vs 6.6%).<sup>28</sup>

It is understandable why undertreated patients had worse outcomes, but why did overtreated patients have worse outcomes? The present study adjusted for severity of illness, comorbidities, and certain processes of care, but it may not have measured certain relevant comorbidities or outcomes. Also, there may have been overtreated patients who had more severe comorbidities than patients who were treated in adherence to the guidelines. It is also curious why the LOS was similar between overtreated patients and those treated in adherence to the guidelines for the first week of hospitalization. This finding may be owing to overtreated patients experiencing complications that did not manifest until after 1 week, such as *Clostridium difficile* colitis.

To our knowledge, the present study is the first to compare outcomes with adherence to the 2007 IDSA/ATS guidelines for CAP in a strictly elderly population. However, there are studies that include populations with a substantial proportion of elderly patients and that also address outcomes in response to adherence to 1 of a variety of guidelines for CAP.<sup>12,29-36</sup> In comparison with studies with mixed-age populations, most of the studies with a substantial proportion of elderly patients show a significantly favorable relationship between guideline compliance and improved outcomes.

In a prospective study evaluating time to clinical stability, Menéndez et al<sup>37</sup> found that their 928 patients who underwent treatment adherent to CAP guidelines were more likely to achieve clinical stability on day 4 of hospitalization than were the 217 patients whose treatment was nonadherent (65.7% vs 54.4%) ( $P < .01$ ). Multivariate analysis also showed that antimicrobial treatment adherent to guidelines was associated with earlier clinical stability (HR, 1.22; 95% CI, 1.04–1.44) ( $P = .01$ ). However, Menéndez et al<sup>37</sup> (1) included patients as young as 18 years in their study, (2) defined *time to clinical stability* according to Halm et al,<sup>38</sup> and (3) used the Spanish antimicrobial treatment guidelines for CAP published in 1998.<sup>39</sup> The Spanish guidelines do not require atypical coverage in hospitalized non-ICU patients as do the 2007 IDSA/ATS guidelines for CAP.<sup>10</sup>

Two retrospective studies found improved outcomes among adult patients who received a regimen adherent to earlier versions of the IDSA or ATS guidelines for CAP. The first study<sup>29</sup> included 631 patients older than 18 years (mean age, 73 years). The authors found a lower mortality rate among patients treated in adherence to the CAP guidelines (3% vs 7%) ( $P = .04$ ), a shorter LOS (5.0 days vs 6.2 days) ( $P < .01$ ), and an equivalent time to clinical stability (2.2 days vs 2.6 days) ( $P = .03$ ). The second study<sup>24</sup> included 780 patients, 20% of whom were outpatients. Univariate analysis revealed an improved mortality rate among patients treated in adherence to the CAP guidelines ( $P < .001$ ), and multivariate analysis revealed a shorter LOS ( $P = .049$ ). Adherence included treatment with the antimicrobials recommended by the guidelines plus more coverage.

Not all studies, however, found an association between guideline adherence and improved outcomes. One study<sup>40</sup> found a similar mortality rate in adherent and nonadherent treatment groups. However, as in any study evaluating outpatients with CAP, the mortality rate was exceedingly low (0.8% vs 0.4%) ( $P = .84$ ). Another study<sup>41</sup> with only 252 outpatients reported an equivalent mortality rate between adherent and nonadherent treatment groups (12% vs 14%) ( $P = .92$ ), but the study's use of the 1993 ATS guidelines, which did not recommend coverage for atypical pathogens in all inpatient populations, may have contributed to the equivalent mortality rates.

One of the strengths of the present study is that we adjusted for severity of illness and processes of care that are known to be associated with mortality. Adjusting for processes of care was especially important because of the international institutions represented. The international population of elderly patients accounts for another strength of the present study: increased generalizability. Another aspect of increased generalizability arises from our inclusion of an international population of elderly patients hospitalized in both ICU and non-ICU settings. An accurate diagnosis of CAP was ensured by our use of radiographic and clinical verification of each case as opposed to relying on billing codes to identify diagnoses. Finally, time to clinical stability had a clear definition and was a pertinent short-term outcome because it is strongly linked to processes of care, while LOS and mortality are affected by factors that may not be directly linked to pneumonia.

The present study has several limitations. Because of its retrospective nature, caution is necessary when interpreting severity-adjusted differences in outcome; additional clinical factors associated with unfavorable clinical outcomes might have been present in the nonadherent treatment population. A prospective study could control for such factors and be designed to explore risk factors for multidrug-resistant pathogens such as *P aeruginosa* and MRSA. However, an institutional review board would not approve a prospective study that included a group of patients to receive less than what is recommended in the 2007 ATS/IDSA guidelines for CAP.<sup>10</sup>

Confounding factors rather than the antibiotic regimen might explain the improved outcomes attributed to guideline adherence. For example, the PSI used in the present study has previously described limitations.<sup>10</sup> An unavoidable confounding factor was the fact that adhering to the treatment guidelines may have been a marker for quality of care in other areas as well. Physicians who treat patients with CAP in adherence to guidelines may also perform other activities that improve the outcomes of their patients. Thirty-day mortality data were not available, so in-hospital mortality was used, which can vary in time (eg, 7 days vs 30 days) and thus potentially introduce a bias.

A limitation inherent in the time period of the present study was the designation of HCAP. Prior to 2005, treatment guidelines for patients admitted to the hospital with risk factors for hospital-acquired pathogens were included in the CAP guidelines.<sup>14</sup> Then in 2005, the ATS and IDSA formally recognized patients with the risk factors for hospital-acquired pathogens as having HCAP and included their treatment in the hospital-acquired pneu-



monia (HAP) guidelines.<sup>42</sup> The move from the CAP to HAP guidelines was not without controversy.<sup>43</sup> Our database was started in 2001, prior to HCAP being described. Among the various criteria for HCAP, the only known criterion recorded in the our database was nursing home status. Incidentally, when nursing home patients were excluded from the database, the statistical results were similar to those found in the present analysis, but a formal study would have to be performed to adequately investigate this issue.

Future studies of elderly patients with CAP are necessary to define what specific drug regimens among those recommended by national guidelines is optimal for this special population. It will also be important to identify the reasons for physicians' nonadherence to guidelines and to investigate the best guideline implementation strategies. Some reasons that have been identified are implementation issues, health care system inefficiency, and severity of illness.<sup>44</sup> Future studies should address feedback as a potentially effective way to improve physician adherence with guidelines.<sup>45,46</sup>

In conclusion, the present study supports using the 2007 IDSA/ATS guidelines for CAP in the elderly because there is a significant beneficial impact on clinical outcomes. Although clinical judgment may indicate the need not to adhere to guidelines when caring for elderly patients with CAP, we recommend that empirical therapy with a spectrum of activity less than what is recommended by the 2007 IDSA/ATS guidelines be avoided.

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