MAJOR ARTICLE

Antibiotic Prescription for Community-Acquired Pneumonia in the Intensive Care Unit: Impact of Adherence to Infectious Diseases Society of America Guidelines on Survival

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(See the editorial commentary by Marrie on pages. 1717–9)

Background. The purpose of our study was to analyze prognostic factors associated with mortality for patients with severe community-acquired pneumonia (CAP).

Methods. We conducted a prospective multicenter study including all patients with CAP admitted to the intensive care unit during a 15-month period in 33 Spanish hospitals. Admission data and data on the evolution of the disease were recorded. Multivariate analysis was performed using the SPSS statistical package (SPSS).

Results. A total of 529 patients with severe CAP were enrolled; the mean age (±SD) was 59.9 ± 16.1 years, and the mean Acute Physiology and Chronic Health Evaluation (APACHE) II score (±SD) was 18.9 ± 7.4. Overall mortality among patients in the intensive case unit was 27.9% (148 patients). The rate of adherence to Infectious Diseases Society of America (IDSA) guidelines was 57.8%. Significantly higher mortality was documented among patients with nonadherence to treatment (33.2% vs. 24.2%). Multivariate analysis identified age (odds ratio [OR], 1.7), APACHE II score (OR, 4.1), nonadherence to IDSA guidelines (OR, 1.6), and immunocompromise (OR, 1.9) as the variables present at admission to the intensive care unit that were independently associated with death in the intensive care unit. In 15 (75%) of 20 cases of *Pseudomonas aeruginosa* infection, the antimicrobial treatment at admission was inadequate (including 8 of 15 cases involving patients with adherence to IDSA guidelines). Chronic obstructive pulmonary disease (OR, 17.9), malignancy (OR, 11.0), previous antibiotic exposure (OR, 6.2), and radiographic findings demonstrating rapid spread of disease (OR, 3.9) were associated with *P. aeruginosa* pneumonia.

Conclusions. Better adherence to IDSA guidelines would help to improve survival among patients with severe CAP. *Pseudomonas* coverage should be considered for patients with chronic obstructive pulmonary disease, malignancy, or recent antibiotic exposure.

Pneumonia is a leading cause of death worldwide. In the United States, it is the sixth most common cause of death and the leading cause of death from infectious diseases. The mortality rate is estimated to be <1% for persons with community-acquired pneumonia (CAP) who do not require hospitalization but as high as 12%–14% among hospitalized patients with CAP. In patients admitted to the intensive care unit (ICU), mortality is 25%–40% [1–3].

At the time that antibiotic treatment needs to be administered, the causal microorganisms generally have yet to be identified. To guide the choice of appropriate initial antibiotic regimen, recommendations for CAP management have been published by various scientific

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societies, including the American Thoracic Society (ATS) [4], the British Thoracic Society [5], the Canadian Infectious Diseases Society [6], the Infectious Diseases Society of America (IDSA) [1, 7], and the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) [8].

The IDSA revised their guidelines in September 2000 [7] and updated them in December 2003 [1]. The antimicrobial agents preferred for patients with CAP who are admitted to the ICU were a β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam, or ertapenem) plus either an advanced macrolide or a respiratory fluoroquinolone; if *Pseudomonas* infection is an issue, an antipseudomonal agent plus ciprofloxacin, or an antipseudomonal agent plus an aminoglycoside plus a respiratory fluoroquinolone or a macrolide are recommended. Risk factors for *Pseudomonas* infection included severe structural lung disease (e.g., bronchiectasis) and recent antibiotic therapy or stay in hospital (especially in the ICU).

Although many of the guidelines are evidence based, there is limited evidence to support the recommendations regarding antimicrobial therapy in the ICU. To the best of our knowledge, validation studies have not focused specifically on patients with severe CAP admitted to the ICU [9–11]; moreover, evaluations of these patients have not taken into account other factors that potentially influence prognosis (e.g., severity of disease at admission, delay in antibiotic administration, comorbidities, and developmental complications).

In the present study, the primary objective was to describe prognostic factors of patients with CAP who were admitted to the ICU. A secondary objective was to evaluate the impact of adherence to IDSA guidelines and of *Pseudomonas aeruginosa* coverage with empirical antimicrobial therapy. Our hypothesis was that the only modifiable prognostic factor at admission in patients with CAP who are admitted to the ICU is antibiotic treatment (e.g., adherence to IDSA guidelines and *P. aeruginosa* coverage).

MATERIALS AND METHODS

One investigator at each hospital prospectively recorded variables in a previously designed database. The data were taken from all patients admitted for CAP to 33 participating hospitals in Spain from 1 December 2000 to 28 February 2002. Informed consent was waived by the ethics committee because of the observational nature of the study. Patients with severe chronic illness or disability in whom pneumonia was an expected terminal event were not included. Patients residing in a nursing home and patients with health care–associated pneumonia were not eligible for enrollment in this study. Patients were admitted to the ICU either to undergo mechanical ventilation or because they were judged to be in an unstable condition requiring intensive medical or nursing care [12]. All patients were followed up during their ICU stay.

The following information was recorded using standardized methods: sex, age, smoking status, alcohol and drug use, comorbidities, initially prescribed antibiotic regimen, time to first antibiotic dose delivery, microbiological findings, etiologic diagnosis, and chest radiograph findings at ICU admission. Intubation and mechanical ventilation requirements, adverse events during ICU stay (e.g., need for vasopressor drugs, ventilator-associated pneumonia, acute renal failure, or empyema), length of stay, radiographic evolution of pneumonia, and patient outcome were also recorded.

Definitions. CAP was defined as an acute lower respiratory tract infection characterized by (1) an acute pulmonary infiltrate evident on chest radiographs and compatible with pneumonia, (2) confirmatory findings of a clinical examination, and (3) acquisition of the infection outside of a hospital, long-term care facility, or nursing home. A patient was considered to be a smoker if he or she had smoked >1 packet per day within the past 10 years [13]. Alcoholism was defined as a consumption of >80 g of alcohol per day within the past 10 years. Immunocompromise was defined as primary immunodeficiency or immunodeficiency secondary to radiation treatment, use of cytotoxic drugs or steroids (daily doses of >20 mg of prednisolone or the equivalent for >2 weeks) [14], or AIDS. Preexisting chronic obstructive pulmonary disease was diagnosed using criteria reported elsewhere [15]. Neurological illness was considered to have occurred if it caused impairment of alertness or confusion. Shock was defined as the need for vasopressors for >4 h after fluid replacement; acute renal failure was defined as a urine output of <20 mL/h or a total urine output of <80 mL in 4 h; rapid radiographic spread was defined as an increase in the size of opacities on chest radiograph by $\geqslant$50% after 48 h.

An organism was considered to be a "definite" etiologic agent only if it could be isolated from samples of blood or pleural fluid or if serological tests revealed a four-fold increase in antibody levels. Isolation of *Pneumocystis jiroveci* or culture of *Legionella pneumophila* or *Mycobacterium tuberculosis* from any of the samples was considered to be the basis of a "definite" diagnosis. Other microorganisms isolated from sputum, tracheal aspirate, protected specimen brush (PSB), or bronchoalveolar lavage fluid samples were considered to be "probable" pathogens. A urinary antigen test result positive for *L. pneumophila* or *Streptococcus pneumoniae* was considered to provide a "probable" etiology [7].

Empirical antibiotic therapy was recorded. Antibiotic prescriptions were left to the discretion of the attending physician and were not protocolized. We specifically asked whether antibiotic prescription was in concordance with IDSA guidelines [1, 7]; this response was then objectively confirmed by an external investigator (M. C. G.).

Time to initial antibiotic treatment was measured in hours

Table 1. Epidemiological characteristics of 529 patients with severe community-acquired pneumonia admitted to 33 intensive care units (ICUs) in Spain.

Variable	All patients (n = 529)	Patients who died during ICU stay (n = 148)	Patients who survived (n = 381)	P
Age, mean years ± SD	59.9 ± 16.1	64.5 ± 13.2	58.2 ± 16.7	<.01
Male sex	380 (71.8)	104 (70.3)	276 (72.4)	>.20
Mean APACHE II score ± SD	18.9 ± 7.4	22.9 ± 7.6	17.4 ± 6.8	<.01
Comorbidity or risk factor				
Alcohol use	135 (25.5)	46 (31.1)	89 (23.4)	.09
Smoking	243 (45.9)	64 (43.2)	179 (47.0)	>.20
Malignancy	37 (7)	16 (10.8)	21 (5.5)	.05
Immunocompromise	64 (12.1)	29 (19.6)	35 (9.2)	<.01
HIV infection	22 (4.2)	8 (5.4)	14 (3.7)	>.20
COPD	196 (37.1)	61 (41.2)	135 (35.4)	>.20
Cardiomiopathy	156 (29.5)	52 (35.1)	104 (27.3)	.09
Neurological Illness	37 (7)	15 (10.1)	22 (5.8)	.11
Diabetes	121 (22.9)	34 (23)	87 (22.8)	>.20
Aspiration	10 (1.9)	3 (2)	7 (1.8)	>.20
Previous antibiotic therapy	126 (23.8)	34 (23)	92 (24.1)	>.20

NOTE. Data are no. (%) of patients, unless otherwise indicated. COPD, chronic obstructive pulmonary disease.

and describes the interval between the time of triage at hospital admission and the initial administration of antibiotics. Appropriate therapy was defined as the use of at least 1 antibiotic to which all isolates were susceptible in vitro or (for *P. jiroveci* or *L. pneumophila*) were expected to be susceptible.

Data analysis. Descriptive analysis was performed. Proportions were compared using the χ^2 test with Yates correction or Fisher's exact test, when necessary. Means were compared using the Student's t test. Values of $P \leqslant .05$ were considered to be significant. Multivariate analysis was performed with the enter backward stepwise elimination logistic-regression analysis model of the SPSS software package, version 11.0 (SPSS); the dependent variable was mortality in the ICU, and independent variables were evaluable variables registered at ICU admission that were associated with death in the ICU in the univariate analysis. To analyze independent factors associated with *Pseudomonas* pneumonia, we performed univariate analysis. The variables significantly associated with *P. aeruginosa* were selected for multivariate analysis.

RESULTS

A total of 529 patients (380 male patients and 149 female patients) were admitted to the 33 ICUs for severe CAP. Mean age (±SD) was 59.9 ± 16.1 years. A total of 148 patients (27.9%) died. The baseline characteristics of the patients are shown in table 1. Patients who died were older (mean age [±SD], 64.5 ± 13.2 years vs. 58.2 ± 16.7 years) and presented with a greater severity of illness at ICU admission (APACHE II score [±SD], 22.9 ± 7.6 vs. 17.4 ± 6.8), compared with patients who survived. The only comorbidity significantly associated with death in the univariate analysis was immunocompromise.

Overall adherence to IDSA guidelines was 57.8% (306 patients). The ICU mortality rate for patients with adherence to IDSA guidelines was lower than for nonadherents (24.2% vs. 33.2%; $P < .05$). There were no statistically significant differences between groups in terms of age (mean age [±SD], 60.8 ± 16.1 years vs. 58.7 ± 16.0 years) or APACHE II score (mean score [±SD], 19.3 ± 7.6 vs. 18.4 ± 7.1). Immunocom-

Table 2. Factors associated with nonadherence to Infectious Diseases Society of America guidelines in 529 patients with severe community-acquired pneumonia.

Variable	Nonadherent group (n = 223)	Adherent group (n = 306)	P
Age, mean years ± SD	58.7 ± 16.0	60.8 ± 16.1	.14
APACHE II, mean score ± SD	18.4 ± 7.1	19.3 ± 7.6	.17
Immunocompromise	48 (22)	16 (5.2)	<.01
COPD	85 (38.1)	111 (36.3)	>.20
Previous receipt of antibiotics	77 (34.5)	49 (16.1)	<.01
Inadequate antibiotic treatment[a]	22/123 (17.9)	19/153 (12.4)	>.20
Receipt of mechanical ventilation	164 (73.5)	185 (60.4)	<.01
Shock	114 (51.1)	156 (50.9)	>.20
Death during ICU stay	74 (33.2)	74 (24.2)	<.05

NOTE. Data are no. (%) of patients, unless otherwise indicated. COPD, chronic obstructive pulmonary disease

[a] No. of patients with inadequate treatment/total patients with known etiology (%).

Table 3. Antibiotic treatment for 529 patients admitted to the intensive care unit (ICU) with severe community-acquired pneumonia.

Variable	All patients (n = 529)	Patients who died during ICU stay (n = 148)	Patients who survived (n = 381)	P
Inadequate antibiotic therapy[a]	41/276 (15)	17/81 (21.5)	24/195 (12.3)	.09
Nonadherence to IDSA guidelines	223 (42.1)	74 (50)	149 (39.1)	<.05
Initial *Pseudomonas aeruginosa* coverage	41 (7.8)	9 (6.1)	32 (8.4)	>.20
Time to initiation of antibiotic therapy, mean h ± SD	6.6 ± 12.2	7.7 ± 13.6	6.2 ± 11.6	>.20

NOTE. Data are no. (%) of patients, unless otherwise indicated. IDSA, Infectious Diseases Society of America.

[a] No. of patients with inadequate treatment/no. of patients with known etiology (%).

promise, recent exposure to antibiotics, and receipt of mechanical ventilation were associated with nonadherence to IDSA guidelines (table 2). Antibiotic regimens prescribed for the group of patients with nonadherence to IDSA guidelines included monotherapy (110 cases), nonpseudomonal coverage (for 32 patients with risk factors for *Pseudomonas* infection), pseudomonal coverage (for 29 patients without risk factors for *Pseudomonas* infection), 3-drug combination antibiotic therapy (27 cases), and other 2-drug combination therapy not recommended by IDSA guidelines (25 cases).

Table 3 shows that nonadherence to IDSA guidelines was associated with ICU mortality in univariant analysis (nonadherence to IDSA guidelines was found in 50% of patients who died and 39.1% of patients who survived; $P < .05$). For 276 patients with a known etiologic diagnosis, receipt of inadequate antibiotic treatment was associated with a nonsignificant increase in mortality (OR, 1.89; 95% CI, 0.95–3.75). Time to initiation of antibiotic therapy was not related to outcome. The ICU-associated mortality rate for patients who received their first dose of antibiotics within 4 h after hospital admission was 26% (75 of 289 patients); for patients who received their first dose >4 h after hospital admission, it was 29.9% (53 of 177 patients; $P > .2$).

Adverse events that occurred during hospitalization in the ICU are shown in table 4. The variables significantly associated with mortality in the ICU were shock, receipt of mechanical ventilation, rapid radiographic spread, acute renal failure, and ventilator-associated pneumonia. A backward stepwise elimination logistic regression analysis was performed, with death during ICU stay as the dependent variable and evaluable variables that were registered at ICU admission as independent variables. Hosmer-Lemeshow C statistic square was 0.69. OR and 95% CI values of independent variables associated with outcome are shown in table 5.

Etiologic diagnosis was established in 276 cases (52.2%). A definite diagnosis was provided by blood culture in 92 cases (33.3%), by pleural fluid culture in 8 (2.9%), and by serological testing in 22 (8%). A diagnosis was provided by tests for urinary antigen detection in 45 cases (16.3%), by culture of bronchoscopic protected specimen brush or bronchoalveolar lavage fluid samples in 28 (10.1%), and by culture of sputum samples or tracheal aspirate specimens in 78 (28.3%). Table 6 shows the pathogens for the overall group (297 patients), the immunocompetent patient subgroup (248), and the immunocompromised patient subgroup (49). Etiological findings for episodes involving inadequate antibiotic treatment are described in table 7. The most frequent causative organism in these cases was *P. aeruginosa* (15 [36.6%] of 41 patients), found

Table 4. Adverse events occurring during intensive care unit (ICU) stay for 529 patients with severe community-acquired pneumonia.

Adverse event	No. (%) of patients: All (n = 529)	Died during ICU stay (n = 148)	Survived (n = 381)	P
Positive blood culture result	108 (20.4)	35 (23.6)	73 (19.2)	>.20
Empyema	32 (6)	5 (3.4)	27 (7.1)	.16
Shock	270 (51)	130 (87.8)	140 (36.7)	<.01
Receipt of mechanical ventilation	349 (66)	142 (95.9)	207 (54.3)	<.01
Rapid radiographic spread	250 (47.3)	106 (71.6)	144 (37.8)	<.01
Acute renal failure	178 (33.6)	109 (73.6)	69 (18.1)	<.01
Ventilator-associated pneumonia	35 (6.6)	20 (13.5)	15 (3.9)	<.01

Table 5. Logistic regression analysis of evaluable variables at intensive care unit (ICU) admission associated with death during ICU stay.

Variable	Odds ratio (95% CI)
Immunocompromise	2.25 (1.2 0–4.21)
Nonadherence to IDSA guidelines	1.66 (1.07–2.57)
APACHE II score, per point	1.12 (1.08–1.16)
Age, years	1.01 (1.00–1.03)

NOTE. IDSA, Infectious Diseases Society of America.

in 8 of 18 patients with and 7 of 23 patients without adherence to IDSA guidelines, followed by *M. tuberculosis* (6 patients) and *Enterobacteriaceae* (5 patients).

Because the antimicrobial treatment at admission was inadequate in 15 (75%) of 20 patients with *P. aeruginosa* infection (including 8 of 15 patients with adherence to IDSA guidelines) and *P. aeruginosa* was the most frequent agent responsible for cases involving inadequate antibiotic treatment, univariate and multivariate analysis were performed to identify factors associated with *P. aeruginosa* infection. Table 8 shows factors independently associated with *P. aeruginosa* infection. Receipt of mechanical ventilation was not associated with *P. aeruginosa* infection. Immunocompromise was present in 20% of patients with *P. aeruginosa* pneumonia and in 15.6% of patients with non-*Pseudomonas* infection ($P > .20$). Chronic obstructive pulmonary disease (OR, 17.9) and malignancy (OR, 11.0) were the comorbidities that were independently associated with severe CAP caused by *P. aeruginosa*.

DISCUSSION

To the best of our knowledge, this is the first study to evaluate the impact of adherence to IDSA guidelines in severe episodes of CAP. Indeed, our study was designed to analyze prognosis factors associated with CAP in the ICU. Multivariate analysis found associations between higher mortality rate and the following factors at ICU admission: age, APACHE II score, immunocompromise, and nonadherence to IDSA guidelines for antibiotic treatment. Adherence to IDSA guidelines was the only potentially modifiable factor for improving the prognosis of patients with CAP who required ICU admission. Only 2 pathogens *(P. aeruginosa* and methicillin-resistant *S. aureus)* were responsible for two-thirds of insufficient initial prescriptions for patients who were treated in accordance with IDSA guidelines.

The aim of clinical guidelines recommended by scientific societies is to facilitate daily clinical practice, improve medical therapies, and reduce variability in treatment [1, 4–8, 16]. In recent years, some authors have analyzed the influence of guidelines on patient prognosis [3, 9–11]. However, there are few reports of the influence of guidelines (especially the IDSA guidelines) on the treatment of severely ill patients. Furthermore, few studies that have evaluated the effect of adherence to IDSA guidelines have adjusted for other prognostic factors, such as age, severity of illness at hospital admission, presence of comorbidities, and pneumonia-associated adverse events during ICU stay.

Marras et al. [10] did not report beneficial effects of guideline compliance on outcomes. However, other recent studies [9, 11]

Table 6. Etiological findings for 276 patients with severe community-acquired pneumonia and microbiological documentation of etiology.

Pathogen	No. (%) of patients		
	All (n = 297)	Immunocompetent (n = 248)	Immunocompromised (n = 49)
Streptococcus pneumoniae	143 (48.1)	126 (50.8)	17 (34.7)
Legionella species	23 (7.7)	20 (8.1)	3 (6.1)
Haemophilus influenzae	22 (7.4)	19 (7.7)	3 (6.1)
Pseudomonas aeruginosa	20 (6.7)	16 (6.5)	4 (8.2)
Methicillin-susceptible *Staphylococcus aureus*	16 (5.4)	12 (4.8)	4 (8.2)
Methicillin-resistant *S. aureus*	3 (1.0)	3 (1.2)	…
Gram-negative bacilli[a]	18 (6.1)	13 (5.2)	5 (10.2)
Pneumocystis jiroveci	10 (3.4)	6 (2.4)	4 (8.2)
Mycobacterium tuberculosis	8 (2.7)	5 (2.0)	3 (6.1)
Varicella-zoster virus	8 (2.7)	8 (3.2)	…
Aspergillus species	1 (0.3)	1 (0.4)	…
Nocardia species	1 (0.3)	…	1 (2.1)
Other[b]	24 (8.1)	19 (7.7)	5 (10.2)

[a] *Klebsiella* species, *Enterobacter* species, *Escherichia coli,* and *Proteus* species.
[b] *Moraxella* species, *Mycoplasma* species, *Streptococcus pyogenes, Streptococcus viridans, Enterococcus* species, cytomegalovirus, and other pathogens.

Table 7. Etiology of episodes of severe community-acquired pneumonia in patients who received inadequate antibiotic treatment.

Pathogen	All patients who received inadequate antibiotic treatment			Immunocompetent patients who received inadequate antibiotic treatment		
	Total (n = 41)[a]	Adherence to IDSA guidelines (n = 18)	Nonadherence to IDSA guidelines (n = 23)	Total (n = 34)	Adherence to IDSA guidelines (n = 16)	Nonadherence to IDSA guidelines (n = 18)
Streptococcus pneumoniae	1 (0.7)	…	1	1	…	1
Legionella species	2 (8.7)	…	2	1	…	1
Haemophilus influenzae	…	…	…	…	…	…
Pseudomonas aeruginosa	15 (75)	8	7	13	7	6
Methicillin-sensitive *Staphylococcus aureus*	1 (6.2)	…	1	1	…	1
Methicillin-resistant *S. aureus*	3 (100)	3	…	3	3	…
Gram-negative bacilli [b]	5 (27.8)	4	1	5	4	1
Pneumocystis jiroveci	3 (30)	…	3	2	…	2
Mycobacterium tuberculosis	6 (75)	1	5	4	1	3
Varicella-zoster virus	3 (37.5)	1	2	3	1	2
Aspergillus species	1 (100)	…	1	1	…	1
Nocardia species	1 (100)	1	…	…	…	…
Other	…	…	…	…	…	…

NOTE. Data are no. of patients with the specified pathogen, unless otherwise indicated. IDSA, Infectious Diseases Society of America.

[a] Data are no. of patients with the specified pathogen who received inadequate antibiotic treatment (percentage of all patients with the specified pathogen who received inadequate antibiotic treatment).

[b] *Klebsiella* species, *Enterobacter* species *Escherichia coli,* and *Proteus* species.

have shown an association between adherence to IDSA or ATS guidelines and lower mortality. Our study found low compliance (57.8%) with IDSA guidelines among patients with severe CAP and higher mortality rates when IDSA guidelines were not followed. Previous reports have shown similar levels of adherence [9, 11, 17]. In some studies [9, 11], the negative effect of noncompliance with guidelines is described in the subset of patients with the most-severe disease (Pneumonia Severity Index risk class V group and patients admitted to the ICU). However, in these studies, the subgroups of patients were small; furthermore, the rates and the effects of previous antibiotic treatment, other epidemiologic factors, and adverse events associated with pneumonia were not evaluated, and these variables could have an influence on adherence to guidelines and on outcome. Moreover, multivariate analysis for studying prognostic factors associated with mortality in these studies does not include other important confounding factors. Mortensen et al. [11] showed a reduction in 30-day mortality among patients hospitalized with pneumonia when antimicrobial therapy was administered in accordance with ATS or IDSA guidelines, especially in patients admitted to the ICU. They adjusted this impact on mortality for other potential confounders (Pneumonia Severity Index, history of chronic obstructive pulmonary disease, time to administration of antibiotics, time to culture of blood samples, and admission to the ICU within the first 24 h after presentation). However, the effects of other factors, such as age, presence of comorbidities, and complications associated with pneumonia (e.g., septic shock and receipt of mechanical ventilation) were not analyzed.

Inadequate therapy is a major risk factor for death [18]. In our study, no patient received recombinant human-activated protein C because it was not commercially available during the study period. However, in the Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis trial [19], the 90-day survival benefit of recombinant human-activated protein C was largely attributable to an 18.1% absolute reduction in mortality rate (from 65% to 47%) for patients who were prescribed inadequate antibiotic therapy; the reduction in mortality rate was limited to only 4% (from 37% to 33%) for patients who were prescribed adequate antibiotic therapy. In the placebo arm, an excess mortality of 28.2% was documented among patients with initial administration of inadequate antibiotics for CAP, compared with patients who received adequate antibiotics (mortality rate, 65% vs. 37%) [20, 21].

Another important finding is the high rate of inadequate

Table 8. Logistic regression analysis of variables associated with severe community-acquired pneumonia due to *Pseudomonas aeruginosa*.

Variable	OR (95% CI)
Chronic obstructive pulmonary disease	17.9 (4.4–73.1)
Malignancy	11.0 (2.2–54.3)
Previous antibiotic treatment	6.2 (1.9–19.3)
Rapid radiographic spread	3.9 (1.1–13.6)

treatment among patients with *P. aeruginosa* pneumonia in the overall group and in the immunocompetent patient subgroup. IDSA and ATS guidelines [1, 4, 7] consider severe structural lung disease, recent antibiotic therapy, and recent stay in the hospital to be risk factors for *P. aeruginosa* infection. In our study, chronic obstructive pulmonary disease, malignancy, previous antibiotic therapy, and rapid radiographic spread were associated with *Pseudomonas* pneumonia. Previously, our group [13] reported that, in the group of patients who underwent intubation, *P. aeruginosa* was the third most frequent etiologic pathogen and suggested that, because of the high mortality rate associated with it, *P. aeruginosa* should be covered in the empirical therapy of all patients undergoing intubation while awaiting results of bacteriological tests. In another prospective study of patients with CAP who required admission to the ICU [22], *P. aeruginosa* was the third most common causative agent, after *S. pneumoniae* and *Legionella* species.

Timely administration of antibiotic agents to hospitalized patients with pneumonia has been associated with improved survival [23] and shorter duration of hospital stay [17] in recent retrospective studies. The latest update of IDSA guidelines [1] recommends initiating antibiotic therapy within 4 h after admission to the hospital for hospitalized patients with CAP (degree of evidence, B-III). In the present study, there were no differences in ICU-associated mortality rate between patients who received their first dose of antibiotic within 4 h after admission to the hospital and those who received it after this time. However, nearly all patients in this study received antibiotics promptly, and if an event happens infrequently, it is difficult to assess its impact.

IDSA guidelines were designed for management of CAP in immunocompetent patients. No significant differences in etiology were found between immunocompromised and immunocompetent patients. For 6 patients whose previous immunodeficiency status was unknown at admission to the ICU, *P. jiroveci* was determined to be the etiologic agent of pneumonia, and further test results were positive for antibodies to HIV. Rello et al. [12] described similar findings in a previous study fifteen years ago. In accordance with these findings, this pathogen should be included in the differential diagnosis of patients who appear to be otherwise healthy who are admitted to the ICU for severe CAP with unknown etiology, and testing for HIV antibodies should be considered.

Several limitations of our study should be taken into account before generalizing our findings. Only 1 investigator judged compliance, and there would be some interobserver variability if >1 reviewer analyzed compliance. In the present study, the overall group included immunocompromised patients, and the IDSA guidelines were designed for the management of CAP only in immunocompetent adults. However, our results included similar rates of inadequate treatment in the overall group and in the immunocompetent subgroup, with comparable etiological findings. Moreover, immunocompromise and nonadherence to IDSA guidelines were independently associated with mortality in the multivariate analysis. The design of our study was multicenter, observational, and nonrandomized, and the results may be subject to particular physician or hospital characteristics. However, a large number of consecutive patients with cases of severe CAP were enrolled at 33 hospitals. The fact that our data on the appropriateness of antibiotic treatment and adherence to guidelines are consistent with prior data suggests that the associations reported here are likely to be generalizable. As in any nonexperimental study, we are unable to state conclusively that the use of guideline-concordant empirical antimicrobial therapy was the cause of decreased mortality in a cohort. However, we have no objective reason to believe that non–guideline-concordant therapy is more likely to be given to patients presenting with more-severe illness. Follow-up of patients after discharge from the ICU was not performed, and our findings may have been different if 90-day or medium-term mortality had been recorded, as in previous studies [24]. Therapeutic changes introduced after the initial antibiotic treatment had been prescribed were not investigated; however, Gleason et al. [25] showed that such changes may not influence the final outcome. The impact on outcome of monotherapy in cases of bacteremic pneumococcal pneumonia was not analyzed; monotherapy was not considered to be inadequate treatment for bacteremic pneumococcal pneumonia, although according to some studies [26], it is associated with worse outcome than combination therapy.

In summary, our findings suggest that adherence to IDSA guidelines is the only modifiable prognosis-related factor for patients with severe CAP. *Pseudomonas* coverage should be considered in patients with chronic obstructive pulmonary disease or malignancy and in patients who have received previous antibiotic therapy.

THE CAPUCI STUDY INVESTIGATORS

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