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Adherence to guidelines' empirical antibiotic recommendations and community-acquired pneumonia outcome

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ABSTRACT: The American Thoracic Society (ATS) published guidelines for the treatment and management of community-acquired pneumonia in 2001, but the impact of adherence on outcomes such as mortality and length of stay is not well defined.

A study of 780 patients with community-acquired pneumonia consecutively admitted to hospital over 1 yr was carried out. Nursing home patients were excluded.

Overall adherence to antibiotics recommended in the ATS guidelines was 84%. The lowest adherence was found in patients admitted to an intensive care unit (52%), especially those at risk of infection with *Pseudomonas aeruginosa* (ATS group IVb). However, very few patients from this group were indeed infected with *P. aeruginosa*. This could be explained by the exclusion of the nursing home patients. There was a difference in mortality between patients that received adherent and nonadherent regimens (3 *versus* 10.6%). There was a difference in length of stay between patients receiving adherent and nonadherent regimens (7.6 *versus* 10.4 days). This result was confirmed on multivariate analysis.

Adherence to the 2001 American Thoracic Society guidelines was high except in community-acquired pneumonia patients admitted to an intensive care unit. Length of stay was shorter in patients who received adherent rather than nonadherent antibiotic regimens.

KEYWORDS: Community-acquired pneumonia, guidelines, mortality, prognosis, treatment

Community-acquired pneumonia (CAP) is an infectious disease that is not routinely reported, making its prevalence difficult to determine. Currently, its reported annual prevalence is 3–5 adults per 1,000 population [1–5]. In the USA, CAP is the sixth leading cause of death and the number one cause of death of infectious origin [3]. In Spain, population studies have shown an annual incidence of 1.62 cases per 1,000 inhabitants [4]. In nonhospitalied patients, CAP mortality is <5%. Among hospitalised patients, CAP mortality ranges 5–15%, and rises to 30% in patients admitted to an intensive care unit (ICU) [6]. Inadequate initial antibiotic treatment is a poor prognostic factor [7–9].

The lack of an aetiological diagnosis when antibiotic treatment needs to be administered, the broad variety of antibiotics available and increasing resistance to antibiotics among the common aetiological pathogens have led different scientific societies to publish clinical guidelines to assist in the selection of the appropriate initial antibiotic regimen, taking into account various risk factors [10–14].

MENENDEZ *et al.* [15] validated the 1993 American Thoracic Society (ATS) guidelines and the 1998 joint guidelines from the Spanish Society of Chemotherapy (SEQ) and the Spanish Society of Pulmonology And Thoracic Surgery (SEPAR) for CAP in a prospective study in Spain, finding a higher adherence to ATS guidelines than to SEQ/SEPAR guidelines, and a higher mortality rate in patients with severe pneumonia in whom one of these guidelines was not followed. HAUCK *et al.* [16] validated a clinical pathway based on the 2000 Infectious Diseases Society of America (IDSA) guidelines [14]. MORTENSEN *et al.* [17] determined that adherence to either the 2001 ATS or 2000 IDSA guidelines may reduce 30-day mortality among patients hospitalised with pneumonia. Two recent retrospective studies, focused on hospitalised patients with CAP, found decreased 48-h [18] and 30-day mortality [19] when initial antibiotic therapy was concordant

For editorial comments see page 823.

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with ATS [12] or IDSA [14] recommendations for these patients. The aim of the present study was to determine the influence of adherence to initial antibiotic recommendations in the 2001 ATS guidelines on mortality and length of stay (LOS). These outcomes were analysed taking into account the risk groups defined in the same guidelines and the initial mortality risk in each patient, as described by the pneumonia severity index (PSI) developed by FINE *et al.* [20]. In addition, patients who were admitted directly from a nursing home were identified and excluded. This was carried out as these patients were considered to have healthcare-associated pneumonia (HCAP), an entity that has been excluded from the CAP patients group, according to the newly published ATS/IDSA guidelines for hospital-acquired pneumonia [21].

It was hypothesised that adherence to empirical antibiotic recommendations of the 2001 ATS guidelines in CAP is associated with a reduction in 30-day mortality and LOS.

MATERIALS AND METHODS

Study population and design

From July 1, 2001 to June 30, 2004, a prospective observational study was conducted at the 800-bed Hospital Clinic of Barcelona (Institut d'Investigacions Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain). The study included all consecutive patients admitted to the emergency department (aged >16 yrs) who showed clinical symptoms of pneumonia accompanied by the appearance of a new pulmonary infiltrate on chest radiography. However, the following patients were excluded: 1) those who had been hospitalised during the previous 21 days; 2) those exhibiting immunosuppression (AIDS or receiving chemotherapy or other immunosuppressive drugs); 3) those who had tuberculosis; 4) those resident in a nursing home; and 5) those with a confirmed alternative diagnosis at the end of follow-up.

Antimicrobial treatment regimen and data collection

The choice of empirical antibiotic therapy was determined entirely by the attending physician. Investigators did not interfere with the decision or enquire about the antibiotic choice. The 2001 ATS guidelines were not publicised among the physicians. All demographic and clinical data, as well as those regarding patient outcome (death and LOS), were recorded using a data collection tool. These data included the following variables: age, sex, residence in a nursing home, any comorbid condition (diabetes mellitus, chronic heart failure, chronic obstructive pulmonary disease, cerebrovascular disease, cancer, liver disease and adrenal disease), physical examination findings on admission (respiratory and cardiac frequency, body temperature, blood pressure and presence of obtundation on arrival), results of initial biochemical analyses (haematocrit, white blood cell count, renal function, electrolyte levels and arterial blood gas levels), chest radiographic findings and antibiotic regimen prescribed.

All surviving patients were visited or contacted by telephone $\geq$30 days after discharge. The ethics committee of the Hospital Clinic of Barcelona approved the present project, and waived the requirement for individual patient consent, since this was a purely observational study.

Definitions

All patients were classified retrospectively into ATS risk groups, according to the 2001 ATS guidelines (table 1) [12], as well as into PSI classes I–V, using the mortality risk scale described by FINE *et al.* [20].

The treatment prescribed during the first 24 h of hospitalisation was considered to be the initial treatment. All initial empirical antimicrobial therapy, whether or not adhering to guidelines, was recorded.

An antibiotic regimen was defined as ATS adherent when the antibiotics chosen by the attending physician followed the recommendations included in the 2001 ATS guidelines, regardless of any additional antibiotic received [12].

Prior antimicrobial treatment received for the current infection in the outpatient setting was also recorded. Prolonged LOS was defined as any stay longer than the 75th percentile of the entire population [16, 22]. Mortality was defined as death during the first 30 days following admission to the emergency department. Confusion was defined as a decreased consciousness or new disorientation regarding person, place or time.

Risk factors for *Pseudomonas aeruginosa* were considered to be the presence of any of the following: structural lung disease such as bronchiectasis; corticosteroid therapy (10 mg·day^{-1} prednisone); broad-spectrum antibiotic therapy for 7 days in the past month; malnutrition; and leukopenic immune suppression (corticosteroid therapy with >10 mg·day^{-1} prednisone and leukopenic immune suppression were also excluding factors) [12].

Microbiological evaluation

Samples considered valid for microbiological evaluation included: 1) sputum, 2) blood culture, 3) pleural fluid culture, 4) urinary *Streptococcus pneumoniae* and *Legionella pneumophila* antigen detection, 5) quantitative culture of tracheobronchial aspirates, 6) protected specimen brush samples, and 7) bronchoalvelolar lavage fluid. Diagnosis of the following microorganisms was performed by means of paired serology at admission and during the third and sixth week thereafter. 1) Respiratory viruses: influenza virus (A and B), parainfluenza virus (1, 2 and 3), respiratory syncytial virus, and adenovirus. 2) Atypical microorganisms, including *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*, as well as *L. pneumophila* serogroup 1 and *Coxiella burnetii*. Urine samples were obtained for detection of *S. pneumoniae* antigen (Binax NOW *Streptococcus pneumoniae* urinary antigen test; Binax, Inc., Portland, ME, USA) and *L. pneumophila* serogroup 1 antigen (Biotest Legionella urine antigen EIA; Biotest, Dreieich, Germany). Processing of samples and diagnostic criteria for a bacterial aetiology have been described elsewhere [23–25].

Statistical analysis

Quantitative variables were compared using an unpaired t-test, and the Mann–Whitney U-test was used for variables that did not follow a normal distribution. Qualitative variables were compared using the Chi-squared test. Two-tailed p-values of <0.05 were considered significant.

Multivariate statistical analyses were performed by logistic regression, with the criteria largest p-value for entering

TABLE 1 American Thoracic Society risk groups and antibiotic choice

Group	Description	Therapy
I	Outpatients with no cardiopulmonary disease or modifying factors	Advanced-generation macrolide (azithromycin or clarithromycin) or doxycycline
II	Outpatients with cardiopulmonary disease and/or other modifying factors	β-lactam (oral cefpodoxime, cefuroxime, high-dose amoxicillin or amoxicillin/clavulanate; or parenteral ceftriaxone followed by oral cefpodoxime) plus either macrolide or doxycycline; or antipneumococcal fluoroquinolone (used alone)
IIIa	Inpatients (not in ICU) with cardiopulmonary disease and/or modifying factors (including being from a nursing home)	Intravenous β-lactam (cefotaxime, ceftriaxone, ampicillin/sulbactam, high-dose ampicillin) plus either intravenous or oral macrolide or doxycycline; or intravenous antipneumococcal fluoroquinolone alone
IIIb	Inpatients (not in ICU) with no cardiopulmonary disease or modifying factors	Intravenous azithromycin alone; if macrolide allergic or intolerant, doxycycline and a β-lactam; or monotherapy with an antipneumococcal fluoroquinolone
IVa	ICU-admitted patients with no risks for *Pseudomonas aeruginosa*	Intravenous β-lactam (cefotaxime, ceftriaxone) plus either intravenous macrolide (azithromycin) or intravenous fluoroquinolone
IVb	ICU-admitted patients with risks for *Pseudomonas aeruginosa*	Selected intravenous antipseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus intravenous antipseudomonal quinolone (ciprofloxacin); or selected intravenous antipseudomonal β-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus intravenous aminoglycoside plus either intravenous macrolide (azithromycin) or intravenous nonpseudomonal fluoroquinolone

ICU: intensive care unit. Data from [12].

variables (0.05) and smallest p-value for removing variables (0.1). Variables remaining in the multivariate analysis model that showed a p-value of $\leqslant 0.05$ were considered significant. Sample size estimates were performed with an α risk of 0.05 and β risk of 0.20.

RESULTS

Patients

A total of 829 patients were studied, 49 of whom came from a nursing home and so were excluded from the subsequent analysis. Of the resultant 780 patients, 138 were treated as outpatients and the rest as in-patients. There were 477 (61.2%) males and 303 (38.8%) females with a mean$\pm$SD age of 64.4$\pm$19.2 yrs (range 16–102 yrs). Their distribution by PSI and ATS risk group are shown in tables 2 and 3. A detailed description of the baseline characteristics of both groups are shown in table 4.

Microbial aetiology by ATS and PSI risk group

In 39.2% of the group as a whole, an aetiological diagnosis was established. The most common pathogen identified was *S. pneumoniae* (19.2%), followed by atypical bacteria (*C. pneumoniae* and *M. pneumoniae*, as well as *L. pneumophila* and *Coxiella burnetii*) as a group (6.4%). When analysed by ATS risk group (table 5), the most common pathogen determined was *S. pneumoniae* in all risk groups, except in ATS risk group I, in which atypical bacteria were most common. Nonfermenting Gram-negative bacteria were uncommon isolates in the present series. *P. aeruginosa* was isolated from only 10 patients (from four as part of mixed infections): six in group IIIa, two in group IIIb, one in group IVa, and one in group IVb. Only two patients died, one in group IIIb and one in group IVa. When analysed by PSI score, the most common pathogen determined was *S. pneumoniae* in all risk groups. Atypical bacteria as a group were second in frequency in all risk groups except PSI V, in which mixed infections were second.

TABLE 2 Distribution by pneumonia severity index class

	All patients	In-patients
Subjects n	780	690
I	133 (17.1)	66 (10.3)
II	136 (17.4)	94 (14.6)
III	130 (16.7)	113 (17.6)
IV	259 (33.2)	248 (38.6)
V	122 (15.6)	121(18.8)

Data are presented as n (%), unless otherwise stated.

TABLE 3 Distribution by American Thoracic Society risk group

	All patients
Subjects n	780
I	126 (16.2)
II	12 (1.5)
IIIa	267 (34.2)
IIIb	304 (39)
IVa	36 (4.6)
IVb	35 (4.5)

Data are presented as n (%), unless otherwise stated.

Antibiotics administered

Antibiotic treatment in patients admitted to hospital included: a combination of a β-lactam (amoxicillin/clavulanic acid,

TABLE 4 Subject demographic and clinical characteristics by community-acquired pneumonia guideline adherence

	Adherent	Nonadherent	OR (95% CI)	p-value
Subjects n	567	123		
Age yrs	64.2±19.4	65.4±18.2		0.54
Males	403 (61.3)	74 (60.2)	1.051 (0.709–1.557)	0.81
ICU admission in first 24 h	37 (5.6)	34 (27.6)	0.156 (0.093–0.262)	<0.001
Mechanical ventilation	21 (3.2)	20 (16.3)	0.170 (0.089–0.325)	<0.001
Pre-existing comorbid conditions				
Active alcohol intake	62 (9.4)	13 (10.6)	0.882 (0.469–1.658)	0.69
Current smoker	194 (29.5)	34 (27.6)	1.097 (0.714–1.685)	0.67
Congestive heart failure	94 (41.3)	20 (16.3)	0.860 (0.508–1.456)	0.57
CPD	302 (46.0)	59 (48.0)	0.923 (0.628–1.357)	0.68
History of stroke	30 (4.6)	6 (4.9)	0.933 (0.380–2.291)	0.88
Chronic liver disease	23 (3.5)	5 (4.1)	0.856 (0.319–2.297)	0.76
History of malignancy	35 (5.3)	7 (5.7)	0.932 (0.404–2.150)	0.87
Chronic renal failure	49 (7.5)	8 (6.5)	1.159 (0.535–2.511)	0.71
Previous antibiotic intake	117 (17.8)	30 (24.4)	0.672 (0.425–1.061)	0.09
Aspiration risk	13 (2.0)	18 (14.6)	0.118 (0.056–0.247)	<0.001
Clinical/laboratory data				
Obtundation	53 (8.1)	23 (18.7)	0.382 (0.224–0.650)	<0.001
Shock	29 (4.4)	16 (13.0)	0.309 (0.162–0.588)	<0.001
f_R >30 breaths·min^{-1}	191 (29.1)	53 (43.1)	0.541 (0.365–0.803)	0.002
SBP <90 mmHg	11 (1.7)	6 (4.9)	0.332 (0.120–0.915)	0.03
DBP <60 mmHg	45 (6.8)	15 (12.2)	0.529 (0.285–0.983)	0.04
f_C >125 beats·min^{-1}	45 (6.8)	8 (6.5)	1.057 (0.486–2.301)	0.89
Temperature <35°C/>40°C	12 (1.8)	2 (1.6)	1.126 (0.249–5.093)	0.88
Arterial pH <7.35	7 (1.1)	5 (4.1)	0.254 (0.079–0.814)	0.013
Arterial S_{a,O_2} <90%	241 (36.7)	63 (51.2)	0.552 (0.374–0.813)	0.02
$P_{a,O_2}/F_{I,O_2}$ <250	111 (16.9)	42 (34.1)	0.392 (0.256–0.600)	<0.001
Haematocrit <30%	24 (3.7)	8 (6.5)	0.545 (0.239–1.243)	0.14
BUN >30 mg·dL^{-1}	112 (17.0)	30 (24.4)	0.637 (0.403–1.008)	0.103
Serum glucose >250 mg·dL^{-1}	47 (7.2)	13 (10.6)	0.652 (0.341–1.245)	0.19
Serum sodium <130 mEq·L^{-1}	46 (7.0)	9 (7.3)	0.954 (0.454–2.002)	0.90
Pleural effusion	73 (11.1)	23 (18.7)	0.543 (0.325–0.909)	0.02
Multilobar infiltrates	111 (16.9)	33 (26.8)	0.554 (0.354–0.868)	0.009
Pneumonia severity index				
Class I–III	353 (53.7)	46 (34.4)	1.994 (1.308–2.888)	0.001[#]
Class IV	213 (32.4)	46 (35.4)		
Class V	91 (13.9)	31 (25.2)		0.004[¶]
CURB ⩾3	83 (12.3)	32 (26.0)	0.411 (0.259–0.654)	<0.001
ICU admission criteria	63 (9.6)	32 (26.0)	0.302 (0.187–0.487)	<0.001

Data are presented as mean±SD or n (%), unless otherwise stated. OR: odds ratio; CI: confidence interval; ICU: intensive care unit; CPD: chronic pulmonary disease; f_R: respiratory frequency; SBP: systolic blood pressure; DBP: diastolic blood pressure; f_C: cardiac frequency; S_{a,O_2}: arterial oxygen saturation; P_{a,O_2}: arterial oxygen tension; F_{I,O_2}: inspiratory oxygen fraction; BUN: blood urea nitrogen; CURB ⩾3: presence of ⩾3 of confusion, urea >7 mm, f_R >30 breaths·min^{-1} and blood pressure (systolic <90 mmHg or diastolic <60 mmHg) at the time of arrival [26]. [#]: OR and 95% CI refers only to class I–III *versus* class IV–V; [¶]: p-value for trend for classes I–V. 1 mmHg=0.133 kPa.

third-generation cephalosporin or carbapenem) and a macrolide (64.2%); quinolones, alone or in combination with macrolides (13.6%); a β-lactam (amoxicillin/clavulanic acid, third-generation cephalosporin or carbapenem) alone (10.4%); a β-lactam and a quinolone (7.8%); macrolides alone (0.6%); other antibiotic combination regimens not including a macrolide or a quinolone (3.3%); and other single-antibiotic regimens (0.2%).

Adherence

In 657 (84.2%) out of 780 patients, and 531 (82.7%) out of 642 patients admitted to a hospital ward or ICU, the initial antibiotic regimen was prescribed in agreement with the guidelines issued by the ATS [12]. Prior ambulatory antimicrobial treatment had been prescribed in 120 (18.7%) out of 642 admitted patients; in these patients, empirical in-patient treatment adhered to ATS guidelines in 93 (77.5%) out of 120

TABLE 5 Microbiological aetiology by American Thoracic Society risk group

	I	II	IIIa	IIIb	IVa	IVb	All patients
Nondiagnostic	93 (73.8)	9 (75.0)	169 (63.3)	169 (55.6)	14 (38.9)	20 (57.1)	474 (60.8)
Streptococcus pneumoniae	12 (9.5)	2 (16.7)	52 (19.5)	70 (23.0)	8 (22.2)	6 (17.1)	150 (19.2)
Atypical bacteria#	12 (9.5)		2 (0.7)	13 (4.3)	0 (0)	1 (2.9)	28 (6.4)
Legionella	3 (2.4)		7 (2.6)	6 (2.0)	3 (8.3)	3 (8.6)	22 (2.8)
Mixed	3 (2.4)		8 (3.0)	20 (6.6)	4 (11.1)	4 (11.4)	39 (5.0)
Virus	1 (0.8)	1 (8.3)	10 (3.7)	16 (5.3)	3 (8.3)		31 (4.0)
Haemophilus influenzae	1 (0.8)		8 (3.0)	4 (1.3)	3 (8.3)	1 (2.9)	17 (2.2)
Other	1 (0.8)		2 (0.7)	4 (1.3)	1 (2.8)		8 (1.0)
Nonfermenting			4 (1.5)	1 (0.3)			5 (0.6)
Staphylococcus aureus			5 (1.9)				5 (0.6)
Enterobacteriaceae				1 (0.3)			1 (0.1)
Total	126	12	267	304	36	35	780

Data are presented as n (%). #: *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Coxiella burnetii*.

patients, compared with 438 (83.9%) out of 522 in the group without prior treatment (p=0.094).

Nonadherent treatments are shown in table 6. In general, it was observed that the nonadherent regimens in ATS groups I–IVa most commonly did not provide for atypical pathogen coverage, whereas most of the nonadherent therapy for ICU-admitted patients in group IVb did not provide coverage for *P. aeruginosa*.

Length of stay

The mean±SD duration of hospital stay was 8.1±7.7 days. In the group adhering to the ATS guidelines, mean duration of hospital stay was 7.6 days, compared with 10.4 days in those receiving treatment nonadherent to the ATS guidelines (table 7). Again, the difference (2.8 days; 95% confidence interval (CI) 0.93–4.66) was significant (p=0.004). LOS was shorter for patients' adherent to the guidelines, except those admitted to the ICU. Stratified by PSI score (table 7), only group IV showed a significant difference in LOS when comparing ATS-adherent and -nonadherent groups (p=0.038).

The cut-off for considering LOS as prolonged in the present study was chosen as 9 days [16, 22]. Prolonged LOS was significantly and independently associated with ATS nonadherence on multivariate analysis (odds ratio (OR) 0.60; p=0.049). Other variables showing significance (table 8) were: respiratory frequency of >40 breaths·min^{-1} at time of arrival (OR 2.51; p=0.035); presence of pleural effusion (OR 3.32; p<0.001); requirement for mechanical ventilation in the first 24 h (OR 5.55; p= 0.001); and active alcohol intake (OR 1.95; p=0.04).

Mortality

The overall mortality rate was 4.1% (33 out of 780). The specific mortality rates among patients receiving adherent and nonadherent regimens were 3.0% (20 out of 657) and 10.6% (13 out of 123), respectively (p<0.001).

The in-patient mortality rate was 5.1% (33 out of 642 admitted patients). The specific mortality rates among admitted patients receiving adherent and nonadherent regimens were 3.8% (20 out of 531) and 11.7% (13 out of 111), respectively (p=0.001). The mortality differences applied to ATS risk group III, but not to risk group IV (table 9), although the number of ICU-admitted patients was small (37 adherent *versus* 34 nonadherent).

When patients were stratified according to PSI score (table 9), mortality was found to be higher in patients receiving

TABLE 6 Treatments nonadherent with American Thoracic Society guidelines by American Thoracic Society risk group

	I–II	IIIa	IIIb	IVa	IVb
β-Lactams alone	12 (100)	36 (80.0)	29 (90.6)	1 (16.7)	1 (3.6)
Other combinations not including a quinolone or a macrolide		8 (17.8)	2 (6.3)	3 (50)	4 (14.3)
Macrolide alone		1 (2.2)			1 (3.6)
Other monotherapies			1 (3.1)		
Quinolone alone				2 (33.3)	2 (7.1)
Non-antipseudomonal β-lactam plus a macrolide					18 (64.3)
Non-antipseudomonal β-lactam plus a quinolone					2 (7.1)

Data are presented as n (%).

TABLE 7 Length of stay (LOS) by adherence to American Thoracic Society (ATS) guidelines in patients stratified by ATS risk group and pneumonia severity index (PSI) score

	Adherent		Nonadherent		Δ (95% CI)	p-value
	Subjects n	LOS days	Subjects n	LOS days		
ATS risk group[#]						
III	494	6.7	77	9.5	2.8 (0.6–5.1)	0.02
IIIa	222	7.1	45	9.2	2.1 (-0.5–4.8)	0.11
IIIb	272	6.3	32	9.8	3.5 (-0.6–7.7)	0.09
IV	37	20.4	34	12.5	-7.9 (-13.7– -2.1)	0.008
IVa	30	20.8	6	20.5	-0.3 (-15–14.4)	0.97
IVb	7	18.6	28	10.8	-7.8 (-18–2.4)	0.11
PSI risk group[¶]						
I	53	6.9	13	8.6	1.7 (-2.8–6.2)	0.45
II	87	5.9	7	8.4	2.5 (-1.4–6.4)	0.21
III	99	6.5	14	8.8	2.3 (-0.6–5.2)	0.12
IV	202	7.9	46	10.9	3.1 (0.2–5.9)	0.04
V	90	10.3	31	11.6	1.2 (-2.1–4.5)	0.46
Total	531	7.6	111	10.4	2.8 (0.93–4.66)	0.004

Δ: difference; CI: confidence interval. [#]: ANOVA for trend in ATS risk group *versus* LOS in days ($p<0.001$); [¶]: ANOVA for trend in PSI risk group *versus* LOS in days ($p<0.001$).

treatment that did not adhere to ATS guidelines in PSI classes III–V, but this did not reach significance.

Logistic regression analysis for the prediction of mortality in admitted patients (table 9) did not confirm ATS adherence as a protective factor. Significant variables were: obtundation (OR 7.04; p= 0.001), shock (OR 5.89; p=0.011), and increased risk of aspiration (OR 2.69; p=0.046).

DISCUSSION

Clinical guidelines recommended by professional societies have been broadly published, and have entered into widespread use in almost every medical field since the 1990s. Until recently there was little evidence of their influence on patient prognosis, or their impact on relevant social and economic variables, such as healthcare-related costs or duration of hospitalisation. GLEASON *et al.* [27] were unable to show significant differences in medical outcomes in CAP outpatients treated according to, or not according to, the 1993 ATS guidelines. MENENDEZ *et al.* [15] only found significant differences in PSI class V patients, whereas two studies from the University of Texas evaluated a combination of the ATS and IDSA guidelines and found a significant difference in both 30-day mortality and LOS [17, 19]. However, these studies were totally retrospective and did not stratify patients according to ATS or IDSA risk group. DEAN *et al.* [28] found decreased mortality and LOS after the implementation of local guidelines based on a combination of local practices and IDSA and ATS guidelines. In the present study, the relationship between antibiotic adherence to the 2001 ATS guidelines for CAP and two important outcomes, mortality and LOS, was examined.

The most important findings of the present study were that adherence to ATS guidelines was high (84.2%), and that there was a significant difference in mortality (3.0 *versus* 10.6%; $p<0.001$) and LOS (7.6 *versus* 10.4 days; p=0.004) between patients receiving adherent and nonadherent regimens, respectively, in the crude analysis. Multivariate analysis confirmed that adherence to ATS guidelines is a protective factor for prolonged LOS, but not for mortality.

The PSI score [20], which estimates the role of 20 clinical factors, is a valid and useful tool for the prediction of mortality in hospitalised patients with CAP. It was observed that mortality in patients admitted to hospital, but not the ICU, increased when the treatment administered was not in accordance with the guidelines. In addition, LOS was shorter for patients treated adherent to the guidelines, except those admitted to the ICU, as reflected in table 7. Stratified by PSI score, only group IV showed a significant difference in LOS, but, using Bonferroni correction, p-values of >0.01 may not indicate a real effect but rather a chance finding due to a multiple-testing effect.

Interestingly, the lowest adherence rate to guideline therapy was in those admitted to the ICU (ATS classes IVa and IVb), for whom adherence was 52.1%. In the present study, the number of patients admitted to the ICU was small, but guideline adherence was not associated with a reduction in mortality or LOS compared with nonadherence to guidelines. Most of the nonadherence for ICU-admitted patients was in group IVb, as no antipseudomonal therapy was provided for those with risk factors. However, very few of the patients were infected with *P. aeruginosa*, and so this nonadherent therapy may in reality have been appropriate therapy, thus explaining the absence of adverse consequences of nonadherence. One reason for such a low rate of *P. aeruginosa* may have been the exclusion of nursing home patients, identifying a need for the re-evaluation of recommendations for group IVb patients when this population excludes those with HCAP.

TABLE 8 Multiple regression analysis for prediction of length of stay (LOS) of >9 days and mortality

	p-value	OR (95% CI)
Variables associated with increased LOS		
Adherence to ATS guidelines	0.049	0.60 (0.36–0.99)
Pneumonia severity index class V	0.053	1.82 (0.99–3.33)
Respiratory frequency >40 breaths·min^{-1}	0.035	2.51 (1.064–5.92)
Serum sodium <130 mEq·L^{-1}	0.06	1.78 (0.98–3.24)
Acute renal failure	0.06	2.02 (0.97–4.19)
Pleural effusion	<0.001	3.32 (1.97–5.59)
Requirement for mechanical ventilation	0.001	5.55 (2.03–15.16)
Active alcohol intake	0.04	1.95 (1.032–3.69)
Variables associated with increased mortality		
Adherence to ATS guidelines	0.486	0.69 (0.25–1.94)
Obtundation	0.001	7.04 (2.22–22.35)
Arterial oxygen saturation <90%	0.056	2.86 (0.97–8.50)
Acute renal failure	0.075	3.28 (0.89–12.18)
Shock	0.011	5.89 (1.51–23.02)
Aspiration	0.046	2.69 (1.02–15.09)

OR: odds ratio; CI: confidence interval; ATS: American Thoracic Society. The variables included in the analysis were as follows: adherence to ATS guidelines; requirement for mechanical ventilation in the first 24 h; intensive care unit (ICU) admission; female sex; age of >65 yrs; chronic renal failure; chronic liver disease; stroke antecedent; diabetes mellitus; respiratory disease; previous antibiotic use; heart failure; active neoplasm; active alcohol intake; active smoking habit; risk of aspiration; belonging to pneumonia severity index class V; positive modified ATS criteria for ICU admission at time of arrival; obtundation; respiratory frequency of >40 breaths·min^{-1}; cardiac frequency of >125 beats·min^{-1}; low blood pressure (systolic blood pressure of <90 mmHg or diastolic blood pressure of <60 mmHg); arterial oxygen saturation of <90%; serum glucose of >250 mg·dL^{-1}; blood urea nitrogen of >30 mg·dL^{-1}; serum sodium of <130 mEq·L^{-1}; haematocrit of <30%; acute renal failure; shock; pleural effusion; and multilobar infiltrate.

The mortality rates obtained in the present study were similar to those reported by other researchers [29, 30]. However, it was found that nonadherence to ATS guidelines was associated with a more than doubling of mortality, although this was not significant on multivariate analysis. Three other studies [31–33] investigating initial empirical treatment according to the ATS guidelines [31, 32] or British Thoracic Society guidelines [33] found no difference in overall mortality between adherence and nonadherence to the three guidelines. Interestingly, differences were specifically found in mortality in ATS group IIIa ($p=0.02$), which represents the majority of patients admitted to a conventional ward (PSI classes III–V). This finding could be related to the lack of coverage for atypicals in some patients belonging to this group (table 6). Recent data from the Community-Acquired Pneumonia Organization project [34] strongly suggest that there is increased mortality in this population when antibiotic treatment does not cover atypical microorganisms.

Multiple regression analysis confirmed that nonadherence to the ATS guidelines is associated with an adverse effect as regards LOS, which supports the utility of implementing these guidelines.

The present lack of mortality benefit on multiple regression analysis may be due to lack of power. With the present findings, a sample size of 1,178 patients was required. However, for LOS, a sample size of only 613 admitted patients was required.

The present conclusions apply to CAP patients in general, but maybe not to those with pseudomonal risks (group IVb), once patients with HCAP have been excluded.

The present study has several potential limitations that should be addressed. First, it is an observational nonrandomised study. This reduces the level of confidence as regards its main finding, *i.e.* in patients with CAP, nonadherence to guidelines increases LOS. Nevertheless, the present authors consider that well-designed observational studies are suited for guideline validation and that randomised controlled trials may not be the best means of performing this type of study, due to ethical issues, overflow from intervention to nonintervention patients, learning abilities, *etc.* Some of these issues have been raised previously by FISHBANE *et al.* [35].

Secondly, since only one process (antibiotic adherence) was being analysed and not composite processes, it was not possible to determine whether or not major adherence is associated with better overall care and how this affected the present results. In addition, the study design does not permit the possibility that treatments not adhering to guidelines may have been chosen for a group of patients with more severe initial disease to be ruled out, despite their belonging to the same risk class as other patients. This is suggested by the finding that patients receiving nonadherent as opposed to adherent treatments, as reflected in table 4, more frequently required ICU admission during the first 24 h (27.6 *versus* 5.6%; $p<0.001$) and mechanical ventilation (16.3.6 *versus* 3.2%; $p<0.001$). They also presented with more aspiration risk (14.6 *versus* 2.0%; $p<0.001$), obtundation (18.7 *versus* 8.1%; $p<0.001$), shock (13.0 *versus* 4.4%; $p<0.001$) and low arterial oxygen tension/inspiratory oxygen fraction ratio at time of arrival (34.1 *versus* 16.9%; $p<0.001$), but the associations with tachypnoea, multilobar infiltrates, blood pressure, arterial oxygen saturation and pH, and pleural effusion are not strong and should be interpreted with caution in order to avoid interpreting chance findings due to a multiple-testing effect as significant, since their p-values are >0.0015. In addition, predefined discharge criteria are lacking. Nevertheless the results of the multivariate analysis suggest an independent impact of guideline adherence as favourably affecting LOS. It can be assumed that the lack of predefined discharge criteria could not lead to a bias that produced a longer LOS in one of the groups since those different discharge criteria should be distributed evenly between the two groups. Comparing the group with a LOS of <9 days and a LOS of >9 days, a higher rate of pneumonia complications was found in the latter group (115 out of 499 *versus* 88 out of 143; OR 5.343 (95% CI 3.595–7.939); $p<0.001$), which could explain the difference in LOS.

Thirdly, the therapeutic changes introduced after the initial antibiotic treatment had been prescribed were not investigated; however, using multivariate analysis, GLEASON *et al.* [36] showed that such changes did not influence final outcome. It is also probable that these changes were not dependent upon

TABLE 9 Mortality by adherence to American Thoracic Society (ATS) guidelines in patients stratified by ATS risk group and pneumonia severity index (PSI) score

	Adherent		Nonadherent		OR (95% CI)	p-value
	Subjects n	Mortality n (%)	Subjects n	Mortality n (%)		
ATS risk group#						
I	114	0 (0)	12	0 (0)		
II	12	0 (0)	0	0 (0)		
III	494	14 (2.8)	77	9 (11.7)	0.22 (0.09–0.53)	<0.001
IIIa	222	11 (5.0)	45	8 (17.8)	0.24 (0.09–0.64)	0.002
IIIb	272	3 (1.1)	32	1 (3.1)	0.35 (0.04–3.43)	0.34
IV	37	6 (16.2)	34	4 (11.8)	1.45 (0.37–5.66)	0.59
IVa	30	5 (16.7)	6	0 (0)		0.28
IVb	7	1 (14.3)	28	4 (14.3)	1.00 (0.09–10.66)	0.99
Total	657	20 (3.0)	123	13 (10.6)	0.27 (0.13–0.55)	<0.001
PSI risk group#						
I	111	0 (0)	22	0 (0)		
II	127	0 (0)	9	0 (0)		
III	115	1 (0.9)	15	1 (6.7)	0.12 (0.01–2.07)	0.09
IV	213	7 (3.3)	46	4 (8.7)	0.36 (0.10–1.27)	0.10
V	91	12 (13.2)	31	8 (25.8)	0.44 (0.16–1.20)	0.10
Total	657	20 (3.0)	123	13 (10.6)	0.27 (0.13–0.55)	<0.001

OR: odds ratio; CI: confidence interval. #: p-value for trend <0.001.

initial adherence, being homogeneously distributed in the present study group.

Fourthly, the time from admission to first antibiotic administration has been suggested as a key predictor of outcome, but this information was not recorded in the present study. Finally, since the present study was carried out in only one hospital, it may not necessarily be possible to extend its results to other settings.

Since the present study was conducted, new CAP guidelines have been published by the ATS and IDSA [37]; however, the therapeutic recommendations are sufficiently similar to those evaluated that it is unlikely that the present findings would have been different had adherence to the new guidelines been evaluated. In addition, the regimens that were nonadherent to the 2001 guidelines would also have been nonadherent to the new guidelines.

In summary, the results of the present study show that adherence to the initial antibiotic recommendations for the empirical treatment of CAP of the 2001 ATS guidelines may contribute to shorter LOS, especially in patients not admitted to the ICU. Therefore, the present data support the recommendations of these guidelines; however, it was found that, once patients with HCAP were omitted, there were very few individuals with *P. aeruginosa* infection, and those with pseudomonal risks who were admitted to the ICU received no benefit from therapy with antipseudomonal agents. These findings suggest a need for the re-evaluation of therapeutic recommendations for ICU-admitted CAP patients with pseudomonal risks, now that patients from nursing homes are not included in this group.

It is also true that the American Thoracic Society/Infectious Diseases Society of America guidelines may not be applicable in many European countries, and correlation of adherence with aetiology is difficult, since an aetiological diagnosis was only obtained in 39.2% of the present patients, 241 of whom exhibited a bacterial aetiology. Of these, 63 (27.5%) out of 229 patients receiving concordant treatment had a length of stay of >9 days compared with eight (66.7%) out of 12 patients receiving discordant treatment (odds ratio 0.190; p=0.004). As regards patients not admitted to the intensive care unit, nonadherence most commonly meant no atypical pathogen coverage, and it was this nonadherent group that exhibited an increased length of stay, which indirectly implies that the American Thoracic Society suggestion that these organisms be covered might be correct, even in Europe.

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REFERENCES

1 Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* 1987; 1: 671–674.

2 Marston BJ, Plouffe JF, File TM Jr, *et al.* Incidence of community acquired pneumonia requiring hospitalization: results of a population based active surveillance study in Ohio. *Arch Intern Med* 1997; 157: 1709–1718.

3 Garibaldi RA. Epidemiology of community-acquired pneumonia in adults: incidence, etiology, and impact. *Am J Med* 1985; 78: 32–37.
4 Almirall J, Bolibar I, Vidal J, *et al.* Epidemiology of community-acquired pneumonia in adults: a population based study. *Eur Respir J* 2000; 15: 757–763.
5 Sobradillo V. Etiología de la neumonía de la comunidad en España. [Aetiology of community-acquired pneumonia in Spain.]. *Arch Bronconeumol* 1993; 29: 365–366.
6 Fine MJ, Smith MA, Carson CA, *et al.* Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. *JAMA* 1995; 274: 134–141.
7 Pachon J, Prados MD, Capote F, Cuello JA, Garnacho J, Verano A. Severe community acquired pneumonia: etiology, prognosis and treatment. *Am Rev Respir Dis* 1990; 142: 369–373.
8 Torres A, Serra-Batlles J, Ferrer A, *et al.* Severe community acquired pneumonia: epidemiology and prognostic factors. *Am Rev Respir Dis* 1991; 144: 312–318.
9 Moine P, Vercken JB, Chevret S, Chastang C, Gajdos P. Severe community acquired pneumonia: etiology, epidemiology and prognostic factors. *Chest* 1994; 105: 1487–1495.
10 Huchon GJ, Gialdroni-Grassi G, Leophonte P, *et al.* Guidelines for management of adult community-acquired lower respiratory tract infections. *Eur Respir J* 1998; 11: 986–991.
11 Zalacaín R, Dorca J, Torres A, *et al.* Tratamiento antibiótico empírico inicial de la neumonía adquirida en la comunidad del adulto inmunocompetente. [Initial empirical antibiotic treatment of community-acquired pneumonia in immunocompetent adults.]. *Rev Esp Quimioter* 2003; 16: 457–466.
12 Niederman MS, Mandell LA, Anzueto A, *et al.* Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *Am J Respir Crit Care Med* 2001; 163: 1730–1754.
13 Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH, the Canadian Community-Acquired Pneumonia Working Group, Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. *Clin Infect Dis* 2000; 31: 383–421.
14 Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine MJ. Guidelines from the Infectious Diseases Society of America: practice guidelines for the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2000; 31: 347–382.
15 Menendez R, Ferrando D, Valles JM, Vallterra J. Influence of deviation from guidelines on the outcome of community-acquired pneumonia. *Chest* 2002; 122: 612–617.
16 Hauck LD, Adler LM, Mulla ZD. Clinical pathway care improves outcomes among patients hospitalized for community-acquired pneumonia. *Ann Epidemiol* 2004; 14: 669–675.
17 Mortensen EM, Restrepo M, Anzueto A, Pugh J. Effects of guideline-concordant antimicrobial therapy on mortality among patients with community-acquired pneumonia. *Am J Med* 2004; 117: 726–731.
18 Mortensen EM, Restrepo MI, Anzueto A, Pugh JA. Antibiotic therapy and 48-hour mortality for patients with pneumonia. *Am J Med* 2006; 119: 859–864.
19 Frei CR, Restrepo MI, Mortensen EM, Burgess DS. Impact of guideline-concordant empiric antibiotic therapy in community-acquired pneumonia. *Am J Med* 2006; 119: 865–871.
20 Fine MJ, Auble TE, Yealy DM, *et al.* A prediction rule to identify low-risk patients with community acquired pneumonia. *N Engl J Med* 1997; 336: 243–250.
21 American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and health care-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171: 388–416.
22 Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. *Arch Intern Med* 2002; 162: 682–688.
23 De Roux A, Marcos MA, Garcia E, *et al.* Viral community acquired pneumonia in nonimmunocompromised adults. *Chest* 2004; 125: 1343–1351.
24 Marcos MA, Jiménez de Anta MT, de la Bellacasa JP, *et al.* Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults. *Eur Respir J* 2003; 21: 209–214.
25 Garcia-Vazquez E, Marcos MA, Mensa J, *et al.* Assessment of the usefulness of sputum culture for diagnosis of community-acquired pneumonia using the PORT predictive scoring system. *Arch Intern Med* 2004; 164: 1807–1811.
26 Neill AM, Martin IR, Weir R, *et al.* Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. *Thorax* 1996; 51: 1010–1016.
27 Gleason PP, Kapoor WN, Stone RA, *et al.* Medical outcomes and antimicrobial costs with the use of the American Thoracic Society guidelines for outpatients with community-acquired pneumonia. *JAMA* 1997; 278: 32–39.
28 Dean NC, Bateman KA, Donnelly SM, Silver MP, Snow GL, Hale D. Improved clinical outcomes with utilization of a community-acquired pneumonia guideline. *Chest* 2006; 130: 794–799.
29 Blanquer J, Blanquer R, Borras R, *et al.* Aetiology of community-acquired pneumonia in Valencia, Spain: a multicentre prospective study. *Thorax* 1991; 46: 508–511.
30 Almirall J, Morato I, Riera F, *et al.* Incidence of community acquired pneumonia and *Chlamydia pneumoniae* infection: a prospective multicentre study. *Eur Respir J* 1993; 6: 14–18.
31 Marras TK, Chan CK. Use of guidelines in treating community-acquired pneumonia. *Chest* 1998; 113: 1689–1694.
32 Schwartz DN, Furumoto-Dawson A, Itokazu GS. Preventing mismanagement of community-acquired pneumonia at an urban public hospital: implications for institution-specific practice guidelines. *Chest* 1998; 113: Suppl. 3, 194S–198S.
33 Hirani NA, Macfarlane JT. Impact of management guidelines on the outcome of severe community acquired pneumonia. *Thorax* 1997; 52: 17–21.
34 Arnold FW, Summersgill JT, Lajoie AS, *et al.* A worldwide perspective of atypical pathogens in community-acquired pneumonia. *Am J Respir Crit Care Med* 2007; 175: 1086–1093.

35 Fishbane S, Niederman MS, Daly C, *et al*. The impact of standardized order sets and intensive clinical case management on outcomes in community-acquired pneumonia. *Arch Intern Med* 2007; 167: 1664–1669.

36 Gleason PP, Meehan TP, Fine JM, Galusha DH, Fine MJ. Associations between initial antimicrobial therapy and medical outcomes for hospitalized elderly patients with pneumonia. *Arch Intern Med* 1999; 159: 2562–2572.

37 Mandell LA, Wunderink RG, Anzueto A, *et al*. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia. *Clin Infect Dis* 2007; 44: Suppl. 2, S27–S72.