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Adherence to guideline's empiric antibiotic recommendations and CAP outcome

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ABSTRACT

The ATS published guidelines for the treatment and management of CAP (2001), but the impact of adherence on outcomes such as mortality and length of stay is not well defined.

We carried out a study of 780 patients with CAP consecutively admitted to the hospital in one year. Nursing home (NH) patients were excluded.

Overall adherence to antibiotics recommended in the ATS guidelines was 84%. The lowest adherence was found in patients admitted to an ICU (52%), especially those at risk for infection with *Pseudomonas aeruginosa* (ATS group IVb). However, very few patients from this group actually were infected with *Pseudomonas aeruginosa*. This could be explained by the exclusion of the NH patients.

There was a difference in mortality between patients that received adherent and non-adherent regimens (3% vs. 10.6%, $p < 0.001$). There was a difference in length of stay (7.6 vs.10.4 days respectively, $p = 0.004$) between patients receiving adherent and non-adherent regimens. This result was confirmed in a multivariate analysis (OR: 0.60; $p=0.049$).

Adherence to the 2001 ATS guidelines was high except in CAP patients admitted to an intensive care unit. Length of stay was lower in patients who received adherent than those receiving non-adherent antibiotic regimens.

INTRODUCTION

Community-acquired pneumonia (CAP) is an infectious disease, not routinely reported, making its real prevalence difficult to determine. Currently, the reported rate is three to five adults per thousand per year [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 incidence of 1.62 cases for 1000 inhabitants per year [4]. In non-hospitalized patients mortality is below 5%. Among hospitalized patients, CAP mortality ranges from 5 to 15%, and rises to 30% in patients admitted to an intensive care unit (ICU) [6]. An inadequate initial antibiotic treatment is a poor prognostic factor [7-9].

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

Menendez and coworkers validated in Spain the 1993 American Thoracic Society (ATS) and the joint 1998 guidelines from the Spanish chemotherapy society (SEQ) and the Spanish pneumonology and thoracic surgery society (SEPAR) for CAP in a prospective study [15], finding a higher adherence to ATS guidelines than to SEQ-SEPAR guidelines, and a higher mortality rate in patient with severe pneumonia in whom one of those guidelines was not followed. Hauck et al validated a clinical pathway based on the 2000 Infectious Diseases Society of America (IDSA) guidelines [14, 16]. Mortensen et al have determined that adherence to either the 2001 ATS or 2000 IDSA guidelines may reduce 30-day mortality among patients hospitalized with pneumonia [17]. Two recent retrospective studies, focused on hospitalized patients with

CAP, found a decreased 48 h [18] and 30 day mortality [19] when initial antibiotic therapy was concordant with the ATS or IDSA [12, 14] recommendations for these patients. The aim of this 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 analyzed taking into account the risk groups defined in the same guideline and the initial mortality risk in each patient, as described by the Pneumonia Severity Index (PSI), developed by Fine et al [20]. In addition, we identified patients who were admitted directly from a nursing home, and excluded them. We did this considering these patients as having healthcare–associated pneumonia (HCAP), an entity that has been excluded from the group of CAP patients, according to the newly published ATS/IDSA guidelines for hospital–acquired pneumonia [21].

We hypothesized that adherence to empiric antibiotic recommendations of the 2001 ATS guidelines in community acquired pneumonia 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, we conducted a prospective observational study at an 800 bed university referral hospital in the city of Barcelona. The study included all consecutive patients (> 16 years of age) admitted to the emergency room who had clinical symptoms of pneumonia accompanied by the appearance of a new pulmonary infiltrate on the chest radiograph. However, we excluded those patients who a) had been hospitalized during the previous 21 days, b) exhibited immunosuppression (AIDS, receiving chemotherapy or other immunosuppressive drugs), c) had tuberculosis, d) were residing in a nursing home, and e) had a confirmed alternative diagnosis at the end of follow-up.

Antimicrobial treatment regimen and data collection:

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

All surviving patients were visited or contacted by telephone 30 days or later after discharge. The Ethics Committee of our institution approved this project, and waived the need for individual patient consent, since this was a purely observational study. .

Definitions:

ATS risk groups: all patients were classified retrospectively according to the 2001 ATS guidelines (Table 1 [12]), as well as by the mortality risk scale described by Fine et al, using PSI classes I-V [20].

We considered the treatment prescribed during the first 24 h of hospitalization 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 in the outpatient setting for this infection 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 in the first 30 days following admission to the emergency room.

Confusion was defined as a decreased consciousness or new disorientation in person, place or time.

Risk factors for *P. aeruginosa* were considered the presence of any of the following: structural lung disease such as bronchiectasis, corticosteroid therapy (10 mg of prednisone per day), broad-spectrum antibiotic therapy for 7 d in the past month, malnutrition, and leukopenic immune suppression (corticosteroid therapy greater than

10 mg of prednisone per day, and leukopenic immune suppression were excluding factors also) [12].

Microbiological evaluation:

Samples considered valid for microbiological evaluation included: 1) sputum; 2) blood culture; 3) pleural fluid culture; 4) urine antigen-detection for *Streptococcus pneumoniae* and *Legionella pneumophila*, 5) quantitative culture of tracheobronchial aspirates; 6) protected specimen brush; 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 syncitial virus (RSA) and adenovirus. 2) "Atypical" microorganisms including: *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* as well as *Legionella pneumophila* serogroup 1 and *Coxiella burnetii*. Urine samples were obtained for detection of *Streptococcus pneumoniae* antigen (Binax NOW *Streptococcus pneumoniae* urinary antigen Test; Binax Inc., Portland, ME, USA) and *Legionella pneumophila* serogroup 1 antigen (BiotestR Legionella Urine Antigen EIA; Biotest, Dreieich, Germany). Processing of samples and diagnostic criteria for a bacterial etiology have been described elsewhere [23 - 25].

Statistical Analysis:

Statistical analysis was carried out using the statistical package Stata 8.0 (College Station, TX) and Grammo 5.2 (Barcelona, Spain). Quantitative variables were compared using the Student T test and Mann-Whitney U test was used in variables that did not follow a normal distribution. Qualitative variables were compared using the Chi-square test. Two tailed p values less of 0.05 were considered significant.

Multivariate statistical analyses were performed by logistic regression, with the criteria p in (0.05), p out (0.1). Variables remaining in the multivariate analysis model that showed $p < 0.05$ were considered significant.

Sample size estimates were performed with alpha risk 0.05 and beta risk 0.20.

RESULTS

Patients:

We studied 829 patients, of whom 49 patients came from a nursing home and were excluded from subsequent analysis, leaving 780 patients, of this group, 138 were treated out of the hospital, and the rest were inpatients. There were 477 (61.2%) men and 303 (38.8%) women, with a mean age of 64.4 (SD 19.2, range 16 to 102 years). Distribution by PSI and ATS risk groups are shown in Table 2. A detailed description of baseline characteristics of both groups are shown in Table 3.

Microbial etiology according to ATS and PSI risk groups:

In the group as a whole, 39.2% had an etiologic diagnosis established. The most common pathogen identified was *Streptococcus pneumoniae* (19.2%), and atypical bacteria (*Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* as well as *Legionella pneumophila* and *Coxiella burnetii*) as a group (6.4%). When we analyzed by ATS risk groups (Table 4) the most common pathogen determined was *Streptococcus pneumoniae* in all risk groups, except in ATS risk group I where atypical bacteria were most common. Non- fermenting Gram-negative bacteria were uncommon isolates in our series. *Pseudomonas aeruginosa* was isolated only in 10 patients (4 as part of mixed infections): 6 in group IIIa, 2 in group IIIb, 1 in group IVa, and 1 in group IVb (only 2 patients died, 1 in group IIIb, and 1 in group IVa). When analyzed by PSI score the most common pathogen determined was *Streptococcus pneumoniae* in all risk groups. Atypical bacteria as a group were second in frequency in all risk groups except in PSI V, where mixed infections where second.

Antibiotics administered:

Antibiotic treatment in patients admitted to the hospital included the combination of a ß-lactam (amoxicillin-clavulanic acid , third-generation cephalosporin, or carbapenem) and a macrolide (64.2%); quinolones, alone or in combination with macrolides (13.6%); a ß-lactam (amoxicillin-clavulanic acid , third-generation cephalosporin, or carbapenem) alone (10.4%); a ß-lactam and a quinolone (7.8%); macrolides alone (0.6%); other combination antibiotics regimens not including a macrolide or a quinolone (3.3%); and other single antibiotic regimens (0.2%).

Adherence:

In 657 of 780 patients (84.2%), and 531 of 642 patients admitted to a hospital ward or intensive care unit (82.7%), 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 of 642 patients (18.7%); in these patients, in hospital empirical treatment adhered to ATS guidelines in 93 of 120 (77.5%), compared with 438 of 522 (83.9%) in the group without prior treatment ($p = 0.094$).

Non-compliant treatments can be seen on table 5. In general, we observed that the non-compliant regimens in ATS groups I- IVa, most commonly did not provide for atypical pathogen coverage, while most of the non-compliant therapy for ICU admitted patients in group IV b, did not provide coverage for *Pseudomona aeruginosa*.

Length of Stay:

The mean duration of hospital stay was 8.1 days (SD 7.7). In the group adhering to the ATS guidelines, mean duration of hospital stay was 7.6 days, compared to 10.4 days in those receiving treatment nonadherent to the ATS guidelines (Table 6). Again, the difference (2.8 days, 95%CI 0.93 to 4.66) was statistically significant ($p = 0.004$). LOS was shorter for patients adherent to the guideline, except those admitted to the ICU.

Stratified by PSI score (Table 6), only group IV showed a statistically significant difference in LOS when comparing ATS adherent and non-adherent groups (p=0.038). The cut off to consider LOS as prolonged in our study was chosen at 9 days [16, 22]. Prolonged LOS was significantly and independently associated to non ATS compliance in the multivariate analysis (OR 0.60 p=0.049). Other variables showing significance (Table 7) where: respiratory rate over 40 at time of arrival (OR 2.51 p=0.035), presence of pleural effusion (OR 3.32 p< 0.001), need for mechanical ventilation in the first 24 hours (OR 5.55 p= 0.001), and active alcohol intake (OR 1.95 p= 0.04).

Mortality:

Overall mortality rate was 4.1% (33/780). Specific mortality rates among patients receiving adherent and non-adherent regimens were 3.0% (20/657) and 10.6% (13/123), respectively (p<0.001).

In-hospital mortality rate was 5.1% (33 of 642 admitted patients). Specific mortality rates among admitted patients receiving adherent and non-adherent regimens were 3.8% (20/531) and 11.7% (13/111), respectively (p=0.001). The mortality differences applied to ATS risk group III, but not to risk group IV, although the number of ICU admitted patients was small (37 adherent vs. 34 non-adherent, Table 8).

When patients were stratified according to PSI score (Table 8), mortality was found to be higher in patients receiving treatment that did not adhere to ATS guidelines in PSI classes III to V but did not reach statistical significance.

Logistic regression analysis to predict mortality in admitted patients (Table 8) did not confirm ATS compliance as a protective factor. Significant variables were: obtundation (OR 7.04 p= 0.001), shock (OR 5.89 p= 0.011) and increased risk for aspiration (OR 2.69 p= 0.046).

DISCUSSION

Clinical guidelines recommended by professional societies have been broadly published and have entered into widespread use over the past few years in almost every medical field. Until recently there was little evidence of their influence on patient prognosis, or their impact on relevant social and economic variables such as health care-related costs or length of hospitalization. Gleason et al were unable to show significant differences in medical outcomes in CAP outpatients treated according to, or not according to, the 1993 ATS guidelines [27]. Menendez et al only found significant differences in PSI class V patients [15], while two studies from the University of Texas evaluated a combination of the ATS and IDSA guidelines and found a significant difference both in 30 day mortality and LOS [17, 19]. However, these studies were totally retrospective and did not stratify patients according to ATS or IDSA risk groups. Dean et al found decreased mortality and LOS after the implementation of a local guideline based in a combination of local practices, and IDSA and ATS guidelines [28].In this study, we examined the relationship between antibiotic adherence to the 2001 ATS guidelines for CAP and two important outcomes: mortality and LOS.

The most important findings in this study were that adherence to ATS guidelines was high (84.2%), and there was a significant difference in mortality (3.0% vs. 10.6%, $p<0.001$) and in LOS (7.6 vs. 10.4 days respectively, $p = 0.004$) between patient receiving adherent and non-adherent regimens 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 to predict mortality in hospitalized patients with CAP. We observed that mortality in patients admitted to the hospital, but not the ICU, increased when treatment

administered was not in accordance to guidelines. Also LOS was shorter for patients adherent to the guideline, except those admitted to the ICU as reflected in table 6. Stratified by PSI score, only group IV showed a statistically significant difference in LOS but using Bonferroni correction p-values over 0.01 may not indicate a real effect, but rather a chance finding due to multiple testing effect.

Interestingly, the lowest adherence rate to guideline therapy was in those admitted to the ICU (ATS class IVa and IVb), where adherence was 52.1%. In our 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 to non-adherence to guidelines. Most of the non-adherence for ICU admitted patients was in group IVb, because no Pseudomonal therapy was provided for those with risk factors. However, very few patients actually were infected with *Pseudomona aeruginosa*, so this "non-compliant" therapy may actually have been appropriate therapy, thus explaining the absence of adverse consequences of non-adherence. One reason for such a low rate of *Pseudomona aeruginosa* may have been our exclusion of nursing home patients, pointing out a need to re-evaluate recommendations for group IVb patients, when this population excludes those with HCAP.

The mortality rates in our study were similar to those reported by other researchers. [29, 30], but we found that non-adherence to ATS guidelines was associated with a more than doubling of mortality, although this was not significant in the multivariate analysis. Three other studies [31 - 33] investigating initial empirical treatment according to the ATS guideline [31, 32] or the British Thoracic Society guidelines [33] were not associated with a difference in overall mortality. Interestingly, we specifically found differences in mortality in group III A of the ATS (p=0.02) which represents the majority of patients admitted to a conventional ward (PSI classes III, IV and V). This

finding could be related to the lack of coverage for atypicals in some patients belonging to this group (see Table 5). Recent data from CAPO project [34] strongly suggest an increased mortality for this population when antibiotic treatment does not cover for atypicals microorganisms.

Multiple regression analysis confirmed that non-adherence to the ATS guidelines is associated with an adverse effect on LOS which supports the utility of implementing these guidelines.

Our lack of mortality benefit in the multiple regression analysis may be due to lack of statistical power. With our findings we needed a sample size of 1178 patients. Regarding LOS, we only needed a sample size of 613 admitted patients.

Our conclusions apply to CAP patients in general, but may be not to those with Pseudomonal risks (group IVb), once patients with HCAP have been excluded.

This study has several potential limitations that should be addressed. First, it is an observational nonrandomized study. This reduces the level of confidence for its main finding, i.e., in patients with CAP, non-adherence to guidelines increases LOS. Nevertheless, we consider that well designed observational studies are suited for guideline validation and that randomized controlled trials may not be the best way to do this type of study, due to ethical issues, overflow from the intervention to non-intervention patients, learning abilities, etc. Some of these issues were raised previously by Fishbane et al [35]. Second, since we were analyzing only one process (antibiotic compliance) and not composite processes, we are not able to tell if major compliance is associated with better overall care and how this affected our results. In addition, the study design does not allow us to rule out the possibility that treatments not adhering to guidelines may have been chosen for a group of patients with more severe initial disease, despite their belonging to the same risk class as other patients. This is

suggested by the finding that **patients receiving non compliant compared to those receiving compliant treatments, as reflected in table 3, required ICU admission during the first 24 hours (27.6% vs. 5.6%, p<0.001) and mechanical ventilation (16.3.6% vs. 3.2%, p<0.001) more often. They also presented more aspiration risk (14.6% vs. 2.0%, p<0.001), obtundation (18.7% vs. 8.1%, p<0.001), shock (13.0% vs. 4.4%, p<0.001), and low PaO2/FiO2 ratio at time of arrival (34.1% vs. 16.9%, p<0.001), but the associations with thaquipnea, multilobar infiltrates, blood pressure, arterial oxygen and pH, and pleural effusion are not strong and should be interpreted with caution in order to avoid interpreting as significative chance findings due to multiple testing effect, as their p values are over 0.0015.** Also we lack predefined discharge criteria. Nevertheless the results of the multivariate analysis suggest an independent impact of guideline adherence on favorably affecting LOS. We can assume that the lack of pre-defined discharge criteria could not lead to a bias that produced a longer LOS in one of the groups as those different discharge criteria should be distributed evenly between both groups. Comparing the group with LOS <9d. and LOS>9 d. we found a higher rate of pneumonia complications in the second group [115/499 vs. 88/143, OR 5.343 (3.595 - 7.939), p<0.001] which could explain the difference in LOS.

Third, 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 the final outcome. Also it is probable that those changes where not dependent on initial adherence, being homogeneously distributed in our study group. Fourth, time from admission to first antibiotic have been suggested as a key predictor of outcome, but this information was not recorded in our

study. Finally, since this study was carried in only one hospital, its results may be not necessarily extend to other settings.

Since we conducted this study, new guidelines for CAP have been published by the ATS and IDSA [37], however, the therapy recommendations are similar enough to the treatments evaluated here, that it is unlikely that the findings would have been different if adherence to the new guidelines was evaluated. In addition, the regimens that were non-compliant with the 2001 guidelines, would also be non-compliant with the new guidelines.

In summary, the results of this study show that adherence to 2001 ATS guidelines initial antibiotic recommendations for the empirical treatment of CAP may contribute to shorter LOS, particularly in patients not admitted to the ICU. Therefore, these data support the recommendations of these guidelines, however, we found that once patients with HCAP were omitted, there were very few individuals who actually had *Pseudomona aeruginosa* infection, and in those with Pseudomonal risks who were admitted to the ICU had no benefit from therapy with anti-Pseudomonal agents. These findings suggest the need to re-evaluate therapy 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 ATS/IDSA guidelines may not be applicable in many European countries, and even thought correlating adherence to etiology is difficult, since we only had an etiologic diagnosis in 39.2% of patients, and in this group found a bacterial etiology in 241 patients. Of those, 63/229 (27.5%) patients with concordant treatment had LOS>9d. compared to patients with discordant treatment [63/229 vs. 8/12 OR 0.190, p=0.004)]. As for non-ICU patients, non-adherence most commonly meant no atypical pathogen coverage, and it was this non-adherent group

that had an increased LOS, which indirectly implies that the ATS suggestion to cover these organisms could be correct, even for Europe.

ABBREVIATIONS

95%CI = 95% confidence interval

AIDS = acquired immunodeficiency syndrome

ATS = American Thoracic Society

CAP = community-acquired pneumonia

COPD = chronic obstructive pulmonary disease

HCAP = healthcare-associated pneumonia

ICU = intensive care unit

IDSA = Infectious Diseases Society of America

LOS = length of stay

OR = odds ratio

PSI = Pneumonia Severity Index

SEPAR = Sociedad Española de Neumología y Cirugía Torácica (Spanish pneumology and thoracic surgery society).

SEQ = Sociedad Española de Quimioterapia (Chemotherapy Spanish Society)

USA = United States of America

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Table 1. American Thoracic Society risk groups and antibiotic choice [12].

Group	Therapy
Group I: **Outpatients, no cardiopulmonary disease, no modifying factors**	Advanced generation macrolide: azithromycin or clarithromycin or Doxycycline
Group II: **Outpatient, with cardiopulmonary disease, and/or other modifying factors**	β-Lactam (oral cefpodoxime, cefuroxime, high-dose amoxicillin, amoxicillin/clavulanate; or parenteral ceftriaxone followed by oral cefpodoxime) plus Macrolide or doxycycline or Antipneumococcal fluoroquinolone (used alone)
Group IIIa: **Inpatients, not in ICU, cardiopulmonary disease and/or modifying factors (including being from a nursing home)**	Intravenous β -lactam (cefotaxime, ceftriaxone, ampicillin/sulbactam, high-dose ampicillin) plus Intravenous or oral macrolide or doxycycline or Intravenous antipneumococcal fluoroquinolone alone
Group IIIb: **Inpatients, not in ICU, no cardiopulmonary disease, no modifying factors**	Intravenous azithromycin alone If macrolide allergic or intolerant: Doxycycline and a β -lactam or Monotherapy with an antipneumococcal fluoroquinolone

Table 1. American Thoracic Society risk groups and antibiotic choice [12], cont

Group IVa: **ICU-admitted patients, no risks for *Pseudomonas aeruginosa***	Intravenous β -lactam (cefotaxime, ceftriaxone) plus either Intravenous macrolide (azithromycin) or Intravenous fluoroquinolone
Group IVb: **ICU-admitted patients, 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

Table 2. Distribution by Pneumonia Severity Index Classes (PSI Class) and

American Thoracic Society (ATS) Risk Groups

PSI Class	Total (n=780)	Admitted (n=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%)

ATS risk groups	All patients (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 number (%)

Table 3. Subject demographic and clinical characteristics by CAP guideline compliance

	ATS adherence						
Variable	Yes (n=567)		No (n=123)		OR	CI	p
Age (years)	64.2	± 19.4	65.4	± 18.2			0.54
Men	403	61.3%	74	60.2%	1.051	0.709-1.557	0.81
ICU admission during first 24 hours	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
Chronic pulmonary disease	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
History, physical examination, laboratory, and radiographic 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
Respiratory rate >30 b.p.m.	191	29.1%	53	43.1%	0.541	0.365-0.803	0.002
Systolic blood pressure <90 mmHg	11	1.7%	6	4.9%	0.332	0.120-0.915	0.03
Diastolic blood pressure <60 mmHg	45	6.8%	15	12.2%	0.529	0.285-0.983	0.04

Table 3. Subject demographic and clinical characteristics by CAP guideline adherence, cont

Heart rate >125 per minute	45	6.8%	8	6.5%	1.057	0.486-2.301	0.89
Temperature <35°C or >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 oxygenation <90%	241	36.7%	63	51.2%	0.552	0.374-0.813	0.02
PaO_2FiO_2 < 250	111	16.9%	42	34.1%	0.392	0.256-0.600	<0.001
Hematocrit <30%	24	3.7%	8	6.5%	0.545	0.239-1.243	0.14
Blood urea nitrogen >30 mg/dl	112	17.0%	30	24.4%	0.637	0.403-1.008	0.103
Serum glucose >250 mg/dl	47	7.2%	13	10.6%	0.652	0.341-1.245	0.19
Serum sodium <130 Meq/l	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 to 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**[a]
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

CURB ≥ 3 = Presence of 3 or more of the following at time of arrival: confusion, urea >7 mmol/l, Respiratory Rate >30/min, blood pressure (systolic <90 mm Hg or diastolic <60 mm Hg) [26]

Data are presented as number (%) or mean ± SD.

** OR, and CI referrers only to group Class I to III vs Class IV to V*

[a] p for trend Classes I, II, III, IV, and V

Table 4. Microbiological etiology by American Thoracic Society risk groups.

	American Thoracic Society Risk Group													
	I		**II**		**IIIa**		**IIIb**		**IVa**		**IVb**		**Total**	
Pathogen	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Non diagnostic	93	(73.8)	9	(75.0)	169	(63.3)	169	(55.6)	14	(38.9)	20	(57.1)	474	(60.8)
S. 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)
H. 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)
Non fermenting	-	-	-	-	4	(1.5)	1	(0.3)	-	-	-	-	5	(0.6)
S. aereus	-	-	-	-	5	(1.9)	-	-	-	-	-	-	5	(0.6)
Enterobacteriaceae	-	-	-	-	-	-	1	(0.3)	-	-	-	-	1	(0.1)
Total	126		12		267		304		36		35		780	

Atypical: M.pneumoniae, C.pneumoniae, C.burnetti.

Table 5 Treatments non-adherent with American Thoracic Society guidelines (n%)

	ATS risk groups				
	I- II	IIIa	IIIb	IVa	IVb
- ß-lactams alone	12 (100%)	36 (80.0%)	29 (90.6%)	1 (16.7%)	1 (3.6%)
- Other combinations not includying 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 ß-lactam plus a macrolide					18 (64.3%)
Non-antipseudomonal ß-lactam plus a quinolone					2 (7.1%)

Table 6. Length of stay according to adherence to American Thoracic Society (ATS) guidelines in patients stratified by ATS risk group and Pneumonia Severity Index (PSI) score.

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

***ANOVA for trend ATS risk group vs. length of stay in days (p<0.001)**

°ANOVA for trend PSI risk group vs. length of stay in days (p < 0.001)

Table 7. Multiple regression analysis to predict length of stay over 9 days and mortality

Variables at risk for increased length of stay	**p**	**O.R.**	**I.C. 95%**
Adherence to ATS guideline	0.049	0.60	0.36 to 0.99
Pneumonia severity score class V	0.053	1.82	0.99 to 3.33
Respiratory Rate > 40 breaths x minute	0.035	2.51	1.064 to 5.92
Serum Sodium < 130 Meq/l	0.06	1.78	0.98 to 3.24
Acute Renal Failure	0.06	2.02	0.97 to 4.19
Pleural effusion	< 0.001	3.32	1.97 to 5.59
Need for mechanical ventilation	0.001	5.55	2.03 to 15.16
Active alcohol intake	0.04	1.95	1.032 to 3.69
Variables at risk for increased mortality	**P**	**O.R.**	**I.C. 95%**
Adherence to ATS guidelines	0.486	0.69	0.25 to 1.94
Obtundation	0.001	7.04	2.22 to 22.35
Oxygen Saturation < 90%	0.056	2.86	0.97 to 8.50
Acute Renal Failure	0.075	3.28	0.89 to 12.18
Shock	0.011	5.89	1.51 to 23.02
Aspiration	0.046	2.69	1.02 to 15.09

Table 7. Multiple regression analysis to predict length of stay over 9 days and mortality, cont

Variables included in the analysis: Adherence to ATS guidelines, need for mechanical ventilation in the first 24 hours, ICU admission, female sex, Age > 65 years, 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 for aspiration, Belonging to Pneumonia Severity Index Class V, Positive Modified ATS criteria for ICU admission at time of arrival, obtundation, respiratory rate > 40 breaths per minute, Cardiac Rate > 125 per minute, Low Blood Pressure (Systolic Blood Pressure

< 90 mmHg or Diastolic Blood Pressure < 60 mmHg), Oxygen Saturation < 90%, serum glucose over 250 mg/dL, serum urea nitrogen >30 mg/dl, serum sodium <130 Meq/l, Hematocrit <30%, acute renal failure, shock, pleural effusion, multilobar infiltrate.

ATS = American Thoracic Society

ICU = intensive care unit

Table 8. Mortality according to adherence to American Thoracic Society (ATS) guidelines in patients stratified by ATS risk group and Pneumonia Severity Index (PSI) score

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

*p test for trend < 0.001