Empiric treatment in hospitalized community-acquired pneumonia. Impact on mortality, length of stay and re-admission

S. Reyes Calzadaa,e, R. Martínez Tomasa,e, M.J. Cremades Romerob, E. Martínez Morágoncé, J.J. Soler Cataluñad, R. Menéndez Villanuevae

a Service of Pneumology, Hospital Universitario La Fe, Valencia, Spain
b Hospital de Gandia, Spain
c Hospital de Sagunto, Spain
d Hospital de Requena, Spain
e Programa de doctorado en medicina, Universidad Autónoma de Barcelona, Spain

Received 17 October 2006; accepted 23 April 2007
Available online 12 July 2007

KEYWORDS
Community-acquired pneumonia; Treatment; Mortality; Length of stay

Summary
Objective: To evaluate adherence to guidelines when choosing an empirical treatment and its impact upon the prognosis of community-acquired pneumonia (CAP).
Methods: A prospective multicentre study was conducted in 425 CAP patients hospitalized on ward. Initial empirical treatment was classified as adhering or not to Spanish guidelines. Adherent treatment was defined as an initial antimicrobial regimen consisting of beta-lactams plus macrolides, beta-lactam monotherapy and quinolones. Non-adherent treatments included macrolide monotherapy and other regimens. Initial severity was graded according to pneumonia severity index (PSI). The end point variables were mortality, length of stay (LOS) and re-admission at 30 days.
Results: Overall 30-day mortality was 8.2%, the mean LOS was 8±5 days, and the global re-admission rate was 7.6%. Adherence to guidelines was 76.5%, and in most cases the empirical treatment consisted of beta-lactam and macrolide in combination (57.4%). Logistic regression analysis showed that other regimens were associated with higher mortality OR = 3 (1.2–7.3), after adjusting for PSI and admitting hospital. Beta-lactam monotherapy was an independent risk factor for re-admission. LOS was independently associated with admitting hospital and not with antibiotics.

0954-6111/S - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2007.04.018
Introduction

Community-acquired pneumonia (CAP) is one of the diseases with the greatest morbidity–mortality in the world, and leads to important consumption of health care resources. The gross mortality rate due to pneumonia is 17.2 per 100,000 inhabitants in Spain,1 versus 20.9 in the United States.2 These figures have not decreased in recent decades.2,3 Mortality due to pneumonia can be related to factors depending on the infection, the causal microorganism, the initial severity of the disease, and parameters associated with medical care. The initial severity of CAP can be quantified, but is not amenable to modification. The causal microorganism is, in turn, dependent upon the geographical setting, patient co-morbidity, toxic habits, and age among others. However, medical intervention is a factor related to the patient prognosis that can be modified and improved. In this context, inadequate initial antibiotic treatment is known to be associated with important mortality.4,5

Prescription of antibiotics in CAP is usually an empirical selection because the causal microorganisms are unknown at diagnosis. Furthermore, neither symptoms nor analytical data or radiological findings allow an accurate etiologic diagnosis. In fact, a limitation on CAP therapy studies is that there are very few well-designed CAP treatment studies and most of them are retrospective and non-experimental.

Guidelines to aid in the decision for empirical treatment and patient management have been developed by scientific societies.6–9 These guidelines stratify patients by age, co-morbidity, risk factors for microbial resistance and/or specific parameters for selecting the antibiotic regimen.

The choice of treatment regimen also has prognostic implications, since different therapeutic protocols exist and not all of them offer the same beneficial effects for the patient.10–12 Thus, treatment adherence to the guidelines, and the use of certain antibiotic regimens such as macrolides plus beta-lactams and fluoroquinolones have been associated with improved outcomes.13–17 However, the controversy remains about the beneficial impact on prognosis of empirical treatments with or without atypical coverage.18,19 Two recently published meta-analyses have shown no beneficial effect when atypical coverage against microorganisms is prescribed.20,21

Our working hypothesis is that mortality, the length of hospital stay, and the course of CAP in hospitalized patients depends on hospital type and the prescription of adequate initial empirical treatment following guidelines. We therefore investigated adherence to the established Spanish guidelines when choosing an empirical antibiotic treatment, and its impact upon the prognosis of patients admitted with CAP.

Patients and methods

A prospective, observational study with a duration of one year was carried out in four public hospitals of the Autonomous Community of Valencia (Spain): a tertiary hospital (Hospital A) attending 400,000 inhabitants, and three district hospitals (B, C and D), respectively, attending 128,000, 125,000 and 54,000 inhabitants. In the tertiary hospital there is a pneumologist on duty, while in the other three hospitals there is an internist physician on duty; a radiologist on duty is found in the four centres.

The study cohort included consecutive patients admitted with CAP. The inclusion criteria were: age >18 years, symptoms of acute respiratory infection, and the presence of a new infiltrate on chest X-ray, with no alternative diagnosis up until resolution. Immunocompromised patients were excluded (human immunodeficiency virus infection (HIV), transplantations, and patients receiving immunosuppressing drug and/or corticosteroids at doses >20 mg/day), as were those with lung abscesses, tuberculosis, suspected aspiration, admission to hospital in the previous 15 days, and patients with pneumonia admitted to Intensive Care Unit (ICU). Informed consent was not required by our local ethics committee because no patient interventions were involved.

A protocol for data collection in the first 24 h was applied in all cases: age, sex, smoking and alcohol consumption, vaccination status, residence for the elderly, co-morbidity (pulmonary, heart, liver, neurological, renal, neoplasms and diabetes mellitus). The following clinical data were recorded: cough, expectoration, chest pain, dyspnea, mental alterations, temperature, heart rate, respiratory rate, and blood pressure. Recorded analytical data were leucocyte count, sodium, potassium, serum creatinine, glucose, GOT/GTP, and arterial blood gas analysis. Radiological parameters were also documented (radiological pattern, number of affected lung lobes, pleural effusion or cavitation). All patients were classified according to the pneumonia severity index (PSI).22

Empiric antibiotic treatment was that one prescribed within the first 24 h. It was classified according to adherence or not to the Spanish guidelines, Sociedad Española de Neumología y Cirugía Torácica (SEPAR)6,7 and to the specific antimicrobial regimen used. Adherence to guidelines for patients hospitalized on ward include the following regimens: beta-lactam (cefotaxime, ceftriaxone or amoxicillin-clavulanate) plus macrolide (clarithromycin, azithromycin, erythromycin), beta-lactam (cefotaxime, ceftriaxone or amoxicillin-clavulanate) in monotherapy, and quinolones (third or fourth generation). Any other antibiotic or combination of antibiotics was considered non-adherent to guidelines. The attending physician prescribed the initial empiric antibiotic therapy. No interventions on prescribing...
physicians were carried out prior or during the study about SEPAR guidelines awareness.

The length of stay (LOS) in hospital was defined as the number of days of patient admission since arrival to hospital until discharge. Follow-up was carried out 30 days after discharge to assess the course of the patient, with evaluation of the need for re-admission, and global mortality at 30 days.

Actual and predicted 30-day mortality were compared for each antibiotic treatment regimen. Actual mortality was calculated dividing the number of deaths by the number of patients given a specific antibiotic treatment. Predicted mortality for the same groups, weighted by severity, was calculated adding the predicted mortality for each patient in the group and dividing by the number of patients in that group. Predicted mortality for each patient was the one assigned to the PSI group in which the patient was classified (I = 0.1%, II = 0.6%, III = 2.8%, IV = 8.2%, V = 29.2%).

Statistical analysis

A descriptive and comparative analysis was performed: univariate analysis was based on the chi-square test for qualitative variables, while the Student’s t-test was used for quantitative variables. Non-parametric tests were used in the absence of a normal distribution. Values of \( p < 0.05 \) were considered statistically significant.

Three multivariate stepwise logistic regression analyses were carried out. Dependent variables were mortality in the first analysis, re-admission in the second, and prolonged LOS (8 days) in the third. The LOS was dichotomized by the median, and prolonged LOS was considered when LOS was >8 days (yes/no). Independent variables in the three analyses were PSI, admitting hospital (A, B, C, D), adherence to guidelines (yes/no) and empiric antibiotic. PSI was dichotomized as high (Fine risk classes IV and V) or low severity (classes I–III). Empiric antibiotic regimens were classified as beta-lactam monotherapy, beta-lactam plus macrolides, quinolones, macrolides monotherapy and others. Odds ratio (OR) and 95% confidence interval (CI) were calculated, and the goodness-of-fit of the models were assessed with the Hosmer–Lemeshow test.

Results

Cohort description

A total of 425 patients were included: 229 (53.9%) admitted to the tertiary centre, and 196 (46.1%) in the general hospitals. The demographic and clinical characteristics are shown in Table 1. There were no significant differences among the four hospitals in terms of co-morbidity, age and sex. However, smoking habit was more frequent in hospitals C and D, \( p = 0.02 \).

Antibiotic regimens

The therapeutic adherent regimens used were: beta-lactam plus macrolide (\( n = 244, 57.4\% \)), beta-lactam monotherapy (\( n = 72, 16.9\% \)), and quinolones (\( n = 11, 2.6\% \)). The non-adherent treatments were classified as macrolide monotherapy (\( n = 32; 7.5\% \)) and others (\( n = 66; 15.5\% \)). The latter included second generation cephalosporins plus macrolides (\( n = 33, 7.7\% \)), ciprofloxacin monotherapy (\( n = 3, 0.7\% \)), ciprofloxacin plus macrolide (\( n = 13, 3.2\% \)) or plus amoxicillin-clavulanate (\( n = 1, 0.2\% \)), third or fourth generation cephalosporins plus amikacin (\( n = 5, 1.1\% \)), imipenem (\( n = 4, 0.9\% \)), second generation cephalosporins as monotherapy (\( n = 3, 0.7\% \)), vancomycin plus macrolide or antipseudomonal cephalosporin (\( n = 3, 0.7\% \)), piperacillin-tazobactam (\( n = 1, 0.2\% \)). The distribution by groups in each hospital is reported in Table 2. The most often used treatment regimen in the four hospitals was the combination of beta-lactams and macrolides. However, this regimen was less frequent in hospital B (38.5%), where an increase was seen in the use of other regimens (31.5%), due to a higher prescription of second-generation cephalosporins plus macrolides. Treatment adherence to the SEPAR guidelines for the global patient cohort was 76.5%. Adherence differed among the hospitals, however, and was seen to be lower in hospitals B (53.4%) and C (67.2%) compared with hospitals A (83.8%) and D (84.6%), \( p = 0.0001 \). The distribution of the antibiotic regimens according to PSI (Table 3) was similar in the low and high-risk groups, except for macrolide monotherapy, which was more frequent among the low-risk patients (13.6% versus 3.2%).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics, co-morbidity and PSI of the study cohort.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ( n (%) )</td>
<td>425</td>
</tr>
<tr>
<td>Age (yr)*</td>
<td>69 ± 16</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>274/151</td>
</tr>
<tr>
<td>Co-morbidity ( n (%) )</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>119</td>
</tr>
<tr>
<td>COPD</td>
<td>143</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>85</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>63</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>23</td>
</tr>
<tr>
<td>Liver disease</td>
<td>23</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>35</td>
</tr>
<tr>
<td>Smoking</td>
<td>77</td>
</tr>
<tr>
<td>Residence for the elderly</td>
<td>18</td>
</tr>
<tr>
<td>PSI ( n (%) )</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>31</td>
</tr>
<tr>
<td>II</td>
<td>52</td>
</tr>
<tr>
<td>III</td>
<td>93</td>
</tr>
<tr>
<td>IV</td>
<td>170</td>
</tr>
<tr>
<td>V</td>
<td>79</td>
</tr>
<tr>
<td>Adherence to SEPAR ( n (%) )</td>
<td>325</td>
</tr>
<tr>
<td>LOS*</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>Deaths ( n (%) )</td>
<td>35</td>
</tr>
<tr>
<td>Re-admission ( n (%) )</td>
<td>32</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SD; M: male; F: female; COPD: chronic obstructive pulmonary disease; PSI: pneumonia severity index; LOS: length of stay; SEPAR: Sociedad Española de Neumología y Cirugía torácica.
Overall mortality was 8.2%, with no significant differences among hospitals. Mortality in adherent group was 26 (8.2%) and in non-adherent group was 9 (8.5%) \( p = 0.9 \), and no differences were found after stratifying for PSI either. The global mortality for each antibiotic regimen and according to PSI is shown in Table 4. No significant differences in global mortality were seen among the different treatment regimens. In the low-risk group, higher mortality was found among the patients treated with beta-lactam monotherapy (7.1%), although it was not statistically significant. In the high-risk group (Fine classes IV – V), mortality was higher in the group administered other regimens (24.3%), \( p = 0.02 \).

A detailed 30-day mortality analysis was made for each antibiotic regimen (Fig. 1). This figure compares actual and predicted mortality rates. Actual mortality for all antibiotic regimens was seen to be lower than the predicted value, except for the other regimens group. In this latter group, actual mortality was greater than predicted from PSI, with a 30.2% increase in deaths.

Length of stay

The median LOS was 8 days. The median LOS in adherent group and in non-adherent group was 8 days, \( p = 0.6 \). On analysing LOS by hospitals, shorter stays were recorded in hospital D, with a median of 6 days, \( p = 0.0001 \). There were no statistically significant differences in LOS with respect to the different antibiotic regimens and PSI, \( p = 0.4 \) (Table 4).

### Table 2

<table>
<thead>
<tr>
<th>Age (yr) (mean±SD)</th>
<th>Beta-lactam +macrolide</th>
<th>Beta-lactam monotherapy</th>
<th>Quinolone</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>70±16</td>
<td>73±14</td>
<td>72±18</td>
<td>55±21</td>
<td>70±16</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>PSI I–III n (%)</th>
<th>PSI IV–V n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactam +macrolide</td>
<td>n = 244 (57%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-lactam monotherapy</td>
<td>n = 72 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinolone</td>
<td>n = 11 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrolide monotherapy</td>
<td>n = 32 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other regimens</td>
<td>n = 66 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>176 (100)</td>
<td>249 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Re-admission

Thirty-two patients were readmitted within 30 days after hospital discharge (7.6%). The re-admission in adherent group was 7 (6.6%) and in non-adherent group was 25 (7.9%), \( p = 0.6 \). The distribution by hospitals was: 17 patients in hospital A (7.5%), 6 in hospital B (8.3%), 6 in hospital C (10.3%), and 3 patients in hospital D (4.6%), \( p = 0.6 \). No significant differences were found in re-admission with respect to the initial treatment regimen used. However, re-admission was related to initial severity (2.1% re-admission in low-risk patients versus 5.4% in the high-risk group), though not to a statistically significant difference (\( p = 0.07 \)) (Table 4).

Multivariate analysis

Three logistic regression analyses were made to predict mortality, re-admission and prolonged LOS. The independent risk factors for mortality were PSI (OR = 11.1, 95% CI 2.6–48.1), and treatment with other regimens (OR = 3, 1.2–7.3). Beta-lactam monotherapy was found to be an independent risk factor for re-admission (OR = 2.7, 1.2–6.1), and in the third model, admission to hospital D was found to be protective for prolonged LOS (OR = 0.2, 0.1–0.5).

Discussion

The most relevant findings of the present study are: (1) the most widely used antibiotic regimen was the combination of beta-lactam plus macrolide, though there was considerable heterogeneity in antibiotic regimens. (2) Rates of adherence to guidelines of the SEPAR were high, but differed among the hospitals. (3) Patients treated with other regimens had an increased mortality risk (OR = 3, 1.2–7.3). (4) Beta-lactam monotherapy was independently associated with re-admission. (5) LOS was not independently influenced by empiric treatment and it was related to the admitting hospital.

The characteristics of study population were similar in all four hospitals, and similar to those of other studies of CAP in hospitalized subjects. The choice of empirical treatment was based on the guidelines of the SEPAR in a large percentage of patients (76.5%), though with differences in adherence among the four hospitals.

The global results show the most common treatment regimen to be the combination of beta-lactam plus macrolide, similar to the findings of other studies. Nevertheless, it should be pointed out that in 9–31% of cases, antibiotic regimens different from those recommended by the Spanish guidelines were used. Thus, in hospital B, more alternative antibiotic regimens were prescribed, due to an increased use of second-generation cephalosporins plus

### Table 4  Mortality, length of hospital stay and re-admission according to antibiotic treatment and PSI.

<table>
<thead>
<tr>
<th>Antibiotic regimen</th>
<th>Mortality n (%)</th>
<th>LOS (median)</th>
<th>Re-admission n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactam+ macrolide</td>
<td>1 (1.1)</td>
<td>20 (13.1)</td>
<td>8</td>
</tr>
<tr>
<td>Beta-lactam monotherapy</td>
<td>2 (7.1)</td>
<td>3 (6.8)</td>
<td>8</td>
</tr>
<tr>
<td>Quinolone</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Macrolide monotherapy</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Other regimens</td>
<td>0</td>
<td>9 (24.3)</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>3 (1.7)</td>
<td>32 (12.9)</td>
<td>8</td>
</tr>
</tbody>
</table>

PSI: Pneumonia severity index; LOS: length of stay.

\( ^{a}p = 0.4 \): comparison median LOS in low-risk patients versus high-risk group.

\( ^{b}p = 0.07 \): comparison re-admission in low-risk patients 2.1% versus 5.4% in the high-risk group.

\( ^{c}p = 0.02 \): in the high-risk group, mortality was greater in the group administered other regimens (24.3%).

![Figure 1](https://via.placeholder.com/150)  
**Figure 1** Actual and predicted 30-day mortality for each antibiotic regimen.
a macrolide. Although this practice does not adhere to Spanish guidelines, it does comply with the previous American guidelines.\textsuperscript{23} Besides inertia to previous practice, Cabana et al.\textsuperscript{7} analysed the reasons for non-adherence to guidelines. They found out many potential barriers to physician guideline adherence, including lack of awareness, familiarity, agreement, self-efficacy and outcome expectancy. In a recent publication, it has been found that other non-pneumologist specialists had a lower adherence to guidelines compared to pneumologists and residents.\textsuperscript{25} Unfortunately, in the current study we have not specifically investigated these reasons.

The distribution of the antibiotic regimens according to PSI was similar in both the low and high-risk groups, with the exception of an increased use of macrolide monotherapy in lowest risk classes.

The mortality rate in our study (8.2%) was similar to that reported by other authors,\textsuperscript{26–29} and was adjusted to the PSI. Noteworthy, mortality was greater (though not statistically significant) in patients administered other regimens. Other authors have previously reported lower mortality when treatment adheres to the guidelines.\textsuperscript{4,13,30}

A detailed analysis of the antibiotic regimens employed in our study shows global mortality to be greater among the patients administered other regimens (13.6% versus 8.2%). On analysing the high-risk patients, mortality among those receiving other regimens was seen to increase significantly (24.3% versus 6.8% and 13.1%). In fact, the difference for each antibiotic regimen between actual and PSI-predicted mortality (Fig. 1) clearly reflects the increased mortality in those treated with other non-adherent regimens. The opposite was observed for the rest of antibiotic regimens, where actual mortality was lower than predicted by PSI. Likewise, other authors\textsuperscript{4,10,14} also reported increased mortality in the group of patients administered other regimens. In the multivariate analysis to predict mortality following adjustment for PSI, other regimens were independently associated to increased mortality (OR = 3, 1.2–7.3).

In the low risk patients, mortality among those treated with macrolides and quinolones as monotherapy was lower than in those administered beta-lactam monotherapy, though statistical significance was not reached. However, these findings should be interpreted with caution, due to the few patients treated with this regimen, and in view of the low mortality inherent to low PSI.

The LOS showed no significant differences for the different antibiotic regimens. In fact, the hospital where the patient was admitted exerted greater influence. The LOS was shorter in hospital D (OR = 0.2, 0.1–0.5), and was unrelated to adherence or non-adherence to the guidelines or to the use of macrolides. Several investigators\textsuperscript{15,31,32} found shorter LOS in patients treated with macrolides, though not all authors corroborate this finding.\textsuperscript{18} Probably, the LOS is more dependent upon factors inherent to the patient and to the hospital involved.\textsuperscript{33–35} Despite differences in LOS among hospitals, we did not find differences on mortality.\textsuperscript{35} A clinical pathway was successful in reducing consumption of resources and LOS without causing adverse effect on mortality and re-admissions.\textsuperscript{36}

The rate of overall re-admission was 7.6%, and tended to be greater among patients given beta-lactam monotherapy, especially in severe CAP (classes IV and V). The multivariate study showed beta-lactam monotherapy to be an independent risk factor for re-admission. Hardly any data are found in the literature on re-admission in CAP and the different antibiotic regimens used.\textsuperscript{37}

Among the limitations of the present study, mention should be made of the few patients treated with quinolones, coincident with the withdrawal of some of these drugs (e.g., trovafloxacin) from the market. Therefore, the results of this group of antibiotics should not be extrapolated to the current situation. Since our study was not randomized, the degree of evidence is not the best, though it would not have been ethical to apply such a design in which a group of patients would be administered antibiotic regimens not recommended by the guidelines.

In conclusion, important adherence to the hospitalized CAP treatment guidelines is observed, though with considerable variability in the empirical antibiotic treatments used in daily clinical practice. Regimens not adhering to the guidelines are associated with greater mortality in CAP and not related to LOS. The beta-lactams are associated with increased re-admission, though further studies are needed to confirm this finding. LOS was related to the hospital more than to the antimicrobial treatment.

References


