Eur Respir J 2006; 27: 1010–1019
DOI: 10.1183/09031936.06.00126004

Impact of initial antibiotic choice on mortality from pneumococcal pneumonia

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ABSTRACT: To determine the impact of initial antimicrobial choice on 30-day mortality rate in patients with community-acquired pneumonia due to *Streptococcus pneumoniae* (CAP-SP), a prospective, observational study was conducted in 35 Spanish hospitals. A total of 638 patients with CAP-SP were identified. Antimicrobials were chosen by the attending physician. Patients were grouped into the following categories: β-lactam monotherapy (n=251), macrolide monotherapy (n=37), β-lactam plus macrolide (n=198), levofloxacin alone/combination (n=48), and other combinations (n=104). The reference category was β-lactam+macrolide.

The 30-day survival probability was 84.9%. Using multivariate survival analysis, factors related to mortality in the entire population were: bilateral disease, suspected aspiration, shock, HIV infection, renal failure and pneumonia severity index (PSI) score Class IV *versus* I–III and categories V *versus* I–III. The association of β-lactams+macrolides was not better than the use of β-lactams alone. The current authors analysed the different groups of patients with significant mortality/morbidity: intensive care unit, PSI Class >III, renal failure, chronic lung disease and bacteraemia. Only in patients with PSI Class >III, who had undergone initial antimicrobial choice classified as other combinations, were associated with higher mortality.

In conclusion, the current authors have not demonstrated an independent association between initial antimicrobial regimen and 30-day mortality in community-acquired pneumococcal pneumonia patients, except for those with a higher pneumonia severity index score.

KEYWORDS: Antimicrobial resistance, mortality, pneumococcal pneumonia, risk factors, *Streptococcus pneumoniae*

The effect of antimicrobial resistance and subsequent discordant antimicrobial therapy (DAT) on prognosis of community-acquired pneumonia due to *Streptococcus pneumoniae* (CAP-SP) has been evaluated in several studies, with conflicting results. Some studies have suggested that antibiotic resistance in *S. pneumoniae* is not clinically relevant [1–3], whereas others [4] have reported higher mortality rates among patients infected with nonsusceptible strains to the administered antibiotics. In a recent study by LUJAN *et al.* [4], it was observed that receiving DAT, as a result of an invasive infection with resistant *S. pneumoniae* isolates, resulted in a significantly higher chance of mortality. In contrast, YU *et al.* [5], reported that DAT, amongst patients with bacteraemic pneumococcal disease who received monotherapy, was only associated with excess mortality when the isolate displayed high-level resistance to cefuroxime, but not with penicillins or cefotaxime.

Several retrospective studies have suggested that the use of a macrolides/β-lactams combination, as part of the initial antimicrobial treatment, for patients with CAP, requiring hospital admission, may shorten the hospital stay [6, 7] and reduce the mortality rate in comparison with those treated with monotherapy [8–10], even when *S. pneumoniae* is finally identified as the causative organism [11–13]. However, many aspects of the apparently beneficial effects of combined therapy remain unclear and/or controversial. There are inconsistencies in reported outcomes and confusing biases that may have influenced these results. For instance, groups receiving the β-lactam/macrolide combination, as opposed to monotherapy, are not comparable with regard to the average prognosis [10]. In a retrospective study on 213 hospitalised patients, BURGESS and LEWIS [14] concluded that it may not be necessary to add a macrolide to a nonpseudomonal third-generation cephalosporin in the initial empirical

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Received:
November 02 2004
Accepted after revision:
January 18 2006

SUPPORT STATEMENT
This study was designed by an *ad hoc* Scientific Committee created by the Sociedad Española de Neumologia y Cirugía Torácica (SEPAR) through its Área de Tuberculosis e Infecciones Respiratorias (TIR). An independent firm (Pharma Consult Madrid) was engaged to carry out the administrative management, the cost of which was paid by AVENTIS. Expenses arising from the study on antibiotic sensitivity of pneumococcal strains and their serotypes, performed in the ''Centro Nacional de Microbiología'' (Majadahonda, Madrid), were supported by a grant from the Fundación RESPIRA, Fundación Española del Pulmón. Data analysis was carried out by the signatory authors of this manuscript with support of the Red-Respira (RTIC C03/11).

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

therapy of CAP. Furthermore, JOHANSEN *et al*. [15] reported that the combination of penicillin–erythromycin is antagonistic to *S. pneumoniae* both *in vitro* and in animal models of invasive disease, suggesting that β-lactam antibiotics and macrolides should not be administered together, unless pneumococcal infection is ruled out. Data from a recent, prospective multicentre study of patients with bacteraemic pneumococcal illness [16], suggests that combination antibiotic therapy improves survival but only among critically ill patients, and without being able to demonstrate any advantage of regimens including macrolides in comparison with nonmacrolide combinations.

In Spain, almost 40% of pneumococci strains express diminished susceptibilty to penicillin and approximately one-third of the isolates are macrolide resistant, most of them having macrolides lincosamides streptogramin-B phenotype [17]. The current authors, therefore, considered that Spain provides a good environment in which to respond to the previously mentioned controversies. Consequently, an observational, multicentre study, on a large series of patients with pneumococcal pneumonia was conducted in Spain to determine the impact of initial antimicrobial therapy and its effect on mortality.

MATERIAL AND METHODS

Patients and study design

From January, 1999 to April, 2000, 638 consecutive adults with CAP-SP were enrolled in 35 Spanish hospitals [17]. A 30-day mortality, from the time of diagnosis, was considered the endpoint of the analysis [18]. Those patients whose 30-day mortality could not be verified (n=66), mainly because they were transferred to other centres, were also included in the analysis with data censored at the date of transfer. Figure 1 shows the Kaplan–Meier plots of patients included in the study.

Diagnostic criteria

CAP was assumed in the presence of acute onset of signs and symptoms, suggesting lower respiratory tract infection and radiographical evidence of a new pulmonary infiltrate that had no other known cause. Microbial investigation techniques, administration of antimicrobial agents and other therapies was left to the discretion of the attending physician. Investigators of every collaborative institution prospectively collected all data according to a standardised protocol. A diagnosis of probable CAP-SP was made in cases where there was a predominance of Gram-positive cocci in pairs and chains, and heavy growth of *S. pneumoniae* in validated sputum and/or tracheobronchial aspirates. A definite diagnosis of pneumococcal pneumonia was considered with one of the following criteria. 1) At least one blood, pleural fluid, or transthoracic needle aspiration culture positive for *S. pneumoniae*. 2) Bacterial growth of $\geqslant 10^3$ colony-forming units (cfu)·mL^{-1} of *S. pneumoniae* from a protected specimen brush and/or $\geqslant 10^4$ cfu·mL^{-1} in bronchoalveolar lavage. 3) Positive urinary antigen for *S. pneumoniae* with a diagnosis of probable pneumococcal pneumonia. The yields of microbial investigations are shown in table 1.

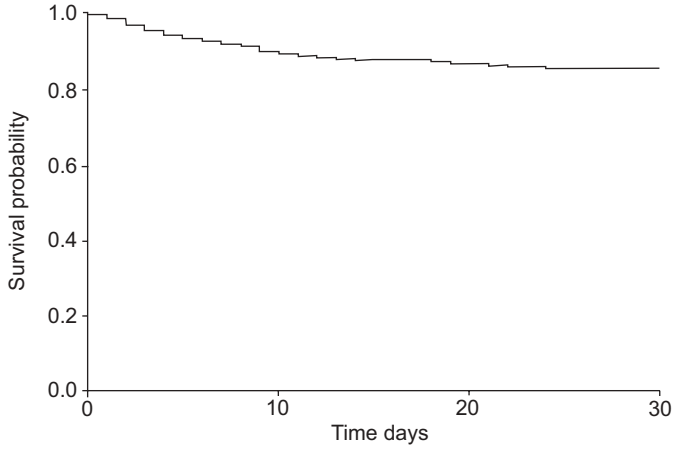

FIGURE 1. Survival analysis. Kaplan–Meier plots of patients included in the study (n=638).

In vitro *susceptibility testing and serotyping*

Pneumococcal isolates from every patient were available for examination. All pneumococcal isolates were submitted to the National Center of Microbiology for serotyping [17, 19, 20] and susceptibility verification, according to the National Committee for Clinical Laboratory Standards 2002 [21]. The following antibiotics were tested: penicillin, amoxicillin, cefuroxime, cefotaxime, imipenem, vancomycin, teicoplanin, erythromycin, tetracycline, chloramphenicol and levofloxacin. Clarithromycin and azithromycin were considered the same as erythromycin in terms of susceptibility and resistance. Ceftriaxone and cefotaxime were also considered equivalent.

Antibiotic therapy

Initial antimicrobial therapy was defined as all antimicrobial agents used at the instance CAP was diagnosed and administered consistently after the first dose until the microbiological results were available. To be eligible for analysis, the daily dose of an antibiotic should have been the minimum dose recommended for treatment of a systemic infection [22].

Patients were divided into cohorts, based on the initial antibiotic regimen. The following all-exclusive antimicrobial

TABLE 1 Diagnostic procedures used in pneumococcal pneumonia

Diagnostic procedure	Procedures undertaken	Positive finding
Sputum	316 (49.5)	181 (28.4)
Bronchial aspirate	108 (16.9)	70 (11)
Blood culture	583 (91.4)	427 (67)
Pleural fluid culture	79 (12.4)	32 (5)
Protected brush catheter	20 (3.1)	14 (2.2)
BAL	19 (3)	8 (1.3)
Transthoracic punction	2 (0.3)	2 (0.3)
Open lung biopsy		
Autopsy	2 (0.3)	
Pneumococcal urinary antigen	68 (10.7)	17 (2.7)
Legionella spp. urinary antigen	160 (25.1)	1 (0.2)
Mycoplasma spp. IgM	109 (17.1)	

All data are presented as n (%). A definite diagnosis of pneumococcal community-acquired pneumonia was achieved in 73% of procedures and a diagnosis of probable pneumococcal pneumonia was recorded in the remaining 27%. BAL: bronchoalveolar lavage; IgM: immunoglobulin M.

TABLE 2 Univariate analysis relative to 30-day mortality

Variables	Cases n	% (95% CI)	HR (95% CI)	p-value[#]	
Antibiotics					
β-Lactams+macrolides	198	31 (27.4–34.6)	1		
Macrolides+					
Second GCS	16				
Third GCS	156				
Fourth GCS	7				
β-Lactam/β-lactamase inhibitor	14				
Imipenem	3				
Others	2				
β-Lactams	251	39.3 (35.6–43.1)	0.66 (0.39–1.10)	0.114	
Second GCS	25				
Third GCS	86				
Fourth GCS	9				
β-Lactam/β-lactamase inhibitor	106				
Imipenem	3				
Others	42				
Macrolides[¶]	37	5.8 (4.1–7.9)	0.15 (0.02–1.13)	0.065	
Levofloxacine	48	7.5 (5.6–9.8)	0.24 (0.06–1.03)	0.054	
Alone	38				
Combination[+]	10				
Other combinations	104	16.3 (13.4–19.2)	2.16 (1.31–3.55)	0.002	<0.001
Second/third/fourth GCS+ aminoglycoside	16				
Any β-lactam+macrolide+aminoglycoside	6				
Aminoglycosides	11				
Antibiotic combinations including					
Vancomycin	5				
Other	66				
Suspected aspiration	51	8 (6.0–10.4)	4.35 (2.69–7.03)		<0.001
Alcohol[§]	144	22.6 (19.3–25.8)	1.60 (1.03–2.48)		0.037
Bilateral pneumonia	99	15.5 (12.7–18.3)	2.95 (1.91–4.56)		<0.001
Change in treatment[ƒ]	107	16.8 (13.9–19.7)	2.26 (1.46–3.51)		<0.001
PSI score					
I+II+III	257	40.3 (36.5–44.1)	1		
IV	234	36.7 (32.9–40.4)	3.77 (1.86–7.68)	<0.001	
V	147	23.0 (19.8–26.3)	10.36 (5.25–20.43)	<0.001	<0.001
ICU admission	125	19.6 (16.5–22.7)	3.52 (2.33–5.31)		<0.001
Shock[##]	102	16.0 (13.1–18.8)	13.56 (8.81–20.87)		<0.001
Tobacco[¶¶]	377	59.1 (55.3–62.9)	0.67 (0.45–1.01)		0.056
Chronic pulmonary disease[++]	254	39.8 (36.0–43.6)	0.59 (0.38–0.93)		0.023
HIV infection[§§]	61	9.6 (7.4–12.1)	1.70 (0.95–3.06)		0.076
Polymicrobial pneumonia[ƒƒ]	34	5.3 (3.7–7.8)	1.74 (0.84–3.59)		0.135
Adequacy of treatment[###]					
Concordant	560	87.8 (85.2–90.3)	1		
Discordant type 1	37	5.8 (4.1–7.9)	1.35 (0.62–2.93)	0.448	
Discordant type 2	41	6.4 (4.6–8.6)	1.70 (0.85–3.39)	0.134	0.268
Penicillin susceptibility					
Sensitive	409	64.1 (60.4–67.8)	1		
Intermediate	164	25.7 (22.3–29.1)	1.46 (0.93–2.30)	0.100	
Resistant	65	10.2 (7.8–12.5)	1.55 (0.82–2.91)	0.175	0.165
Typical symptomatology[¶¶¶]	106	16.6 (13.7–19.5)	2.09 (1.32–3.32)		0.002
Renal failure[+++]	127	19.9 (16.8–23)	5.06 (3.36–7.62)		<0.001
Bacteraemia	429	67.2 (63.6–70.9)	1.03 (0.67–1.59)		0.898

TABLE 2 (Continued)

Variables	Cases n	% (95% CI)	HR (95% CI)	p-value#	
Serotype					
A§§§	142	22.3 (19.0–25.5)	1		
Bfff	428	67.1 (63.4–70.7)	90330 (0)	0.846	
C####	68	10.7 (8.3–13.1)	159235 (0)	0.838	0.087

95% CI: 95% confidence interval; HR: hazard ratio; GCS: generation cephalosporin; PSI: pneumonia severity index [23]; ICU: intensive care unit. #: For those variables with several categories the first column of p-values compares every category of the variable to reference category, assigning a p-value of 1 to the reference category. The second column shows the significance of the variable as a whole. ¶: Erythromycin, clarithromycin or azithromycin. +: Third and fourth GCS (n=4) or other (n=6). §: Estimated daily consumption of >80 g of alcohol for at least the preceding year. f: Modifications in the route of administration and/or step-down therapy were not considered as a change in antimicrobial therapy. ##: Blood pressure ⩽90 mmHg not corrected by *i.v.* fluids, or requiring pressor medication. ¶¶: Smokers were defined as current smokers even if they had quit <6 months before the beginning of the study. ++: Chronic obstructive pulmonary disease, chronic bronchitis, bronchiectasis and chronic pulmonary conditions other than asthma. §§: Infection by HIV was recovered of the previous chart information and by the data on admittance. ff: Mixed infections were established when another likely microorganism was identified along with at least one of the following: 1) At least a four-fold increase in immunoglobulin G titres for *Chlamydophila pneumoniae*, *Legionella pneumophila, Coxiella burnetii*, *Mycoplasma pneumoniae*, and respiratory viruses; 2) positive urinary antigen for *L. pneumophila*; 3) identification of other bacterial pathogen according to standard methods in samples other than sputum or bronchial aspirate. ###: Antibiotic treatment was considered concordant if at least one antibiotic, administered during the first 48 h after the specimen was obtained for culture, showed full *in vitro* sensitivity (neither intermediate nor resistant) against the isolated strains. Therapies without this criterion were defined as discordant and classified as either type 1, when pneumococcal strains showed intermediate susceptibility to the administered therapy, or type 2, when the infection was caused by pneumococcal strains resistant to the administered regimen. ¶¶¶: When at least three of the following were present: cough, expectoration, pleuritic pain, fever and onset or increase of dyspnoea. +++: Serum creatinine>1.5 mg·dL^{-1} and/or blood urea nitrogen>20 mg·dL^{-1} in previously normal patients. §§§: Serotypes 1, 5, 8, 10, 13, 17, 18A, 18F, 20, 23F, 25, 34, 37, 38, 42 showed no mortality. fff: Serotypes 3, 4, 6A, 6B, 7, 9N, 9V, 11, 12, 14, 15A, 15F, 16, 18C, 22, 23A, 23B, 31, 33, 35, NT had a mortality rate of 17%. ####: Serotype 19 pneumococcal isolate had a mortality rate of 27.6% [17].

agent categories were established: β-lactam monotherapy (n=251), macrolide monotherapy (n=37), β-lactam+macrolide (n=198), levofloxacin alone (n=38) or in combination (n=10), and other combinations (n=104). The reference category therapy was β-lactam+macrolide, as it is one of the most broadly accepted and commonly used options for patients with moderate-to-severe CAP. Days on antibiotics (oral/*i.v.*) were also evaluated. Antibiotic treatment was considered concordant if at least one antibiotic administered during the first 48 h, after the specimen was obtained for culture, showed full *in vitro* sensitivity (neither intermediate nor resistance) against the isolated strains. Therapies without this criterion were defined as discordant and classified as: Type 1, when pneumococcal strains showed intermediate susceptibility to the administered therapy; or Type 2, when the infection was caused by pneumococcal strains resistant to the administered regimen.

Statistical analysis

For the primary end-point, a cumulative 30-day mortality was used (dependent variable). The independent variables were chosen as those found previously, according to the literature, to be associated with mortality (table 2). Categorical variables were compared using the Fisher's exact and the Chi-squared tests, with Yates' correction when necessary. Survival curves were constructed according to the methods of Kaplan and Meier, and comparisons of the survival curves were performed with a two-sided log-rank test. Multivariate analyses were performed with the use of a Cox proportional-hazards regression model to identify variables that were independently predictive of outcome [24]. Those variables showing an association with survival in the univariate analysis with significance level of $p<0.2$ were included in the Cox model. Data were analysed using computer software. Institutional review board approval was obtained according to local requirements.

RESULTS

Patient characteristics

The study population was composed of 638 patients. The mean (range) patient age was 61.58 yrs (18–97) and 64.7% were male. The variables included in the analysis are presented in table 2.

Diagnosis of pneumococcal pneumonia

Of the *S. pneumoniae* isolates, 427 out of the 638 (67%) patients were recovered from blood samples (table 1). Serological samples were taken from 340 (53.3%) patients on admission and 204 (32%) during convalescence. Overall, 195 (30.6%) patients had paired samples. Mixed infections were present in 34 (5.4%) patients. The most important were: influenza A/B virus (n=14), *Escherichia coli* (n=4), coagulase-positive staphylococci (n=4), *Haemophilus influenzae* (n=3), *Legionella* spp. (n=3), and *Chlamydophila pneumoniae* (n=3). Overall, six patients presented infections with three organisms, and 24 with two organisms. All mixed infections were adequately treated, except for those cases in which viruses were involved.

Microbiological pattern

The proportion of pneumococcal isolates with diminished susceptibility to antibiotics was: penicillin 35.7% (10.2% high-level resistance), cefuroxime 32%, cefotaxime 2.8%, imipenem 26.3%, levofloxacin 0.6% and 27.4% showed a minimum inhibitory concentration (MIC) to erythromycin of 128 μg·mL^{-1} [17].

Initial antimicrobial therapy

Overall, 59 specific antimicrobial regimens were prescribed in this series. Amoxicillin/clavulanate was the most commonly

TABLE 3 The initial empirical antimicrobial choice according to adequacy of treatment and baseline severity of illness, as measured by pneumonia severity index (PSI) score, and its relation to mortality

Empirical therapeutic option	Patients n (%)	Concordant treatment[#]	PSI score I–III		PSI score IV, V	
			Patients	30-day mortality[¶]	Patients	30-day mortality[+]
β-Lactams+macrolides	198 (31)	94.4 (90.3–97.2)	72 (36.4, 29.7–43.5)	6 (8.3, 3.1–17.3)	126 (63.6, 56.5—70.3)	25 (19.8, 13.3–27.9)
β-Lactams	251 (39.3)	86.5 (82.2– 90.7)	109 (43.4, 37.3–49.6)	2 (1.8, 0.2–6.5)	142 (56.6, 50.4–62.7)	25 (17.6, 11.7– 24.9)
Macrolides	37 (5.8)	64.9 (47.5–79.8)	24 (64.9, 47.5–79.8)	1 (4.2, 0.1– 21.1)	13 (35.1, 20.2–52.5)	0
Levofloxacin (mono/polytherapy)	48 (7.5)	100 (92.6– 100)	22 (45.8, 31.4–60.8)	0	26 (54.2, 39.2– 68.6)	2 (7.7, 0.9–25.1)
Other combinations	104 (16.3)	80.8 (71.9– 87.8)	30 (28.8, 20.4–38.6)	1 (3.3, 0.1–17.2)	74 (71.2, 61.4–79.6)	30 (40.5, 29.3– 52.6)
	638 (100)	87.8 (85.2– 90.3)	257 (40.3, 36.5–44.1)	10 (3.9, 1.8– 7)	381 (59.7, 55.9–63.5)	82 (21.5, 17.4– 25.6)

Data are presented as n (%), n (95% confidence intervals (%)) or n (%, 95% CI). Antibiotic treatment was considered concordant if at least one antibiotic administered during the first 48 h after the specimen was obtained for culture showed full *in vitro* sensitivity (neither intermediate nor resistant) against the isolated strains. [#]: $p<0.0001$; [¶]: $p=0.203$; [+]: $p=0.001$.

used monotherapy regimen (n=106, 16.6% patients) and therapy with a third-generation cephalosporin+macrolide was the most frequent combination with 156 regimens (24.5%). The initial antimicrobial choice according to baseline severity of illness, as measured by pneumonia severity index (PSI) [23] and mortality, is summarised in table 3. Almost two-thirds (63.6%) of β-lactam+macrolide combinations were prescribed for patients with PSI Class IV–V, whereas 64.9% of macrolide-monotherapy regimens were prescribed for patients with PSI Class I–III. As a result of the high levels of resistance to macrolides in this series, DAT was more frequently found among patients receiving these antimicrobials ($p<0.0001$, table 3). There were subsequent changes in the antimicrobial regimen in 107 patients. In all of these patients, the initial therapy was modified 48 h after beginning the treatment. Changes in the initial antibiotic selection were not significantly associated with a 30-day mortality.

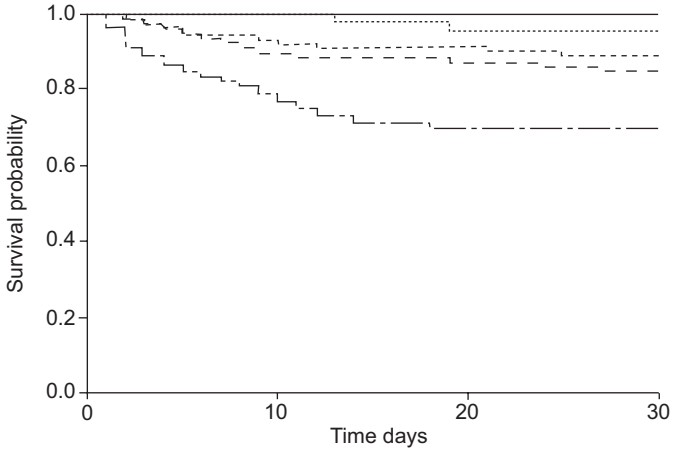

FIGURE 2. Survival analysis. Kaplan–Meier plots according to different antibiotic regimens (n=638 patients). ——: macrolide; ·····: levofloxacin; - - - -: β-lactam; – – – –: β-lactam+macrolide; – - – - –: other combinations.

Mortality and empirical antimicrobial selection for the entire population

The 30-day survival probability of the current cohort was 84.9% (95% CI 82–7). The mean follow-up of patients who died was 10.3 days (median 8.5). A total of 78 (12.1%) patients received DAT (type 1 or 2) and 16 (20.5%) died. This variable was not associated with an increase in mortality in the univariate analysis (table 2). Survival analysis by antibiotic therapy groups (Kaplan–Meier plots) is shown in figure 2. The multivariate analysis of factors related to mortality is shown in table 4. Neither resistance to penicillin nor the initial empirical

TABLE 4 Survival multivariate analysis relative to 30-day mortality for the whole study population[#]

Variables	HR (95% CI)	p-value[¶]	
Antibiotics			
β-Lactams+macrolides	1		
β-Lactams	1.02 (0.58–1.81)	0.945	
Macrolides	0.62 (0.08–4.66)	0.638	0.268
Levofloxacin	0.26 (0.06–1.12)	0.069	
Other combinations	1.27 (0.72–2.20)	0.421	
Suspected aspiration	2.79 (1.55–4.99)		0.001
Bilateral pneumonia	1.98 (1.24–3.17)		0.004
PSI score			
I+II+III	1		
IV	2.61 (1.25–5.42)	0.010	
V	3.24 (1.51–6.94)	0.002	0.010
Shock	5.76 (3.41–9.75)		<0.001
HIV infection	2.06 (1.11–3.83)		0.022
Renal failure	1.86 (1.11–3.12)		0.019

HR: hazard ratio; PSI: pneumonia severity index. For the full definition of each variable refer to table 2. [#]: n=638 patients; [¶]: for those variables with several categories the first column of p-values compares every category of the variable to the reference category. The second column shows the significance of the variable as a whole. HR p-values were calculated using Cox regression models; for further explanations see Methods section.

antimicrobial regimen or its concordance, were significantly related to mortality. Although the empirical antimicrobial choice was associated with mortality on univariate analysis, statistical significance disappeared upon the multivariate analysis. Using the β-lactam+macrolide combination as the reference category for initial antimicrobial therapy, only macrolides and levofloxacin showed hazard ratio (HR) <1. An encouraging trend in the multivariate analysis stands out in reference to mortality when levofloxacin is used, although the sample size is small (48 patients) and is not statistically significant (table 4).

In order to make the class of β-lactams more homogeneous, the current authors performed a restricted analysis on patients treated with amoxicillin/clavulanate or non-pseudomonal third-generation cephalosporin, alone or in combination with a macrolide. Mortality for monotherapy/combination was 10.8 and 15.1% (Fisher's exact test 0.237), respectively. Some authors [7, 8, 11] have suggested that penicillins are inferior to cephalosporin monotherapy or as the β-lactam component of combination therapy. However, the present authors did not observe any significant difference when patients receiving amoxicillin monotherapy were compared with those receiving cephalosporin monotherapy (Fisher's exact test 0.538).

The following factors were significantly associated with mortality when survival analysis (Cox regression model) was applied: bilateral disease (HR 1.98, 95% CI 1.24–3.17, p=0.004), aspiration (2.79, 1.55–4.99, p=0.001), shock (5.76, 3.41–9.75, p<0.0001), HIV infection (2.06, 1.11–3.83, p=0.022), renal failure (1.86, 1.11–3.12, p=0.019) and PSI score categories I–III *versus* IV (2.61, 1.25–5.42, p=0.010) and categories I–III *versus* V (3.24, 1.51–6.94, p=0.002; table 4). Regarding initial antimicrobial choices or mortality rates, the current authors have not found significant differences among hospitals in the current series.

Mortality and empirical antimicrobial selection for selected groups of patients

For the purpose of clinical interest, and because it has been assessed in several previous publications, factors related to mortality were analysed using the same protocol as that for the entire population. This was performed on the following groups of patients. 1) Patients admitted to the intensive care unit (ICU), mortality 32.8%. 2) Patients with PSI Class >III, mortality 21.5%. 3) Patients who developed renal failure during the current episode, mortality 37.8%. 4) Patients with chronic lung disease, mortality 10.6%. 5) Patients who contracted bacteraemia, mortality 14.5% (table 5).

Three points should be noted here. First, in patients with PSI Class >III (n=381), the initial antimicrobial choice referred to as other combinations, presented a statistically significant association with mortality (HR 2, 95% CI 1.2–3.4, p=0.013). Secondly, when the current authors considered the antimicrobial choice as an overall variable in this group of patients, the p-value was also significant (p=0.039, table 5). Thirdly, in those patients who developed renal failure during the episode, penicillin susceptibility is significantly related to mortality (table 5).

TABLE 5 Survival multivariate analysis in selected groups

Variables	HR (95% CI)	p-value#	
ICU¶			
Antibiotics			
β-Lactams+macrolides	1		
β-Lactams	0.45 (0.18–1.22)	0.116	
Macrolides	0	0.984	
Levofloxacin	0.73 (0.1–5.6)	0.762	0.082
Other combinations	1.84 (0.9–3.6)	0.074	
Shock	3.7 (1.5–8.8)		0.004
Renal failure	3.2 (1.5–7)		0.003
Typical symptoms	2.3 (1.1–5.2)		0.038
PSI Class >III+			
Antibiotics			
β-Lactams+macrolides	1	0.187	
β-Lactams	1.49 (0.8–2.7)	0.967	0.039
Macrolides	0	0.162	
Levofloxacin	0.36 (0.08–1.5)	0.013	
Other combinations	2 (1.2–3.4)		
Bilateral pneumonia	2.28 (1.4–3.7)		0.001
Shock	6.5 (4.1–10.3)		<0.001
HIV infection	2.24 (1.2–4.2)		0.014
Renal failure§			
Antibiotics			
β-Lactams+macrolides	1		
β-Lactams	0.51 (0.2–1.2)	0.136	
Macrolides	1.9 (0.2–14.8)	0.537	
Levofloxacin	0.3 (0.04–2.4)	0.245	0.094
Other combinations	1.5 (0.8–2.9)	0.249	
Bilateral pneumonia	2.3 (1.2–4.5)		0.015
Shock	6 (2.7–13.1)		<0.001
Penicillin susceptibility			
Sensitive	1		
Intermediate	2.9 (1.4–6)	0.004	
Resistant	2.9 (1.2–7.3)	0.023	0.006
Typical symptoms	2.7 (1.2–6.1)		0.014
Chronic lung disease‡			
Antibiotics			
β-Lactams+macrolides	1		
β-Lactams	0.6 (0.3–1.5)	0.323	
Macrolides	0	0.986	
Levofloxacin	0	0.961	0.771
Other combinations	1.2 (0.5–3.2)	0.711	
Shock	7.6 (3.5–16.3)		<0.001
Bacteraemia##			
Antibiotics			
β-Lactams+macrolides	1		
β-Lactams	1.2 (0.6–2.4)	0.576	
Macrolides	0.8 (0.1–6.5)	0.867	
Levofloxacin	0.3 (0.04–2.5)	0.275	0.226
Other combinations	1.8 (1–3.4)	0.053	
Bilateral pneumonia	2.2 (1.3–3.9)		0.005
PSI score			
I+II+III	1		
IV	3.4 (1.3–8.6)	0.010	
V	5.6 (2.3–13.8)	<0.001	0.001
Shock	7.7 (4.3–13.9)		<0.001
Typical symptoms	2.4 (1.3–4.3)		0.004

HR: hazard ratio; 95% CI: 95% confidence interval; PSI: pneumonia severity index. For the full definition of each variable refer to table 2. #: For those variables with several categories the first column of p-values compares every category of the variable to the reference category. The second column shows the significance of the variable as a whole. ¶: n=125; +: n=381; §: n=127; ‡: n=254; ##: n=429; HR p-values were calculated by Cox regression models; for further explanations see Methods section.

DISCUSSION

In the current study the authors have assessed the relationship between empirical antibiotic treatment and mortality in

CAP-SP patients following two different strategies: 1) the analysis of the population as a whole, and 2) the analysis of those groups of patients of particular interest, due to their mortality/morbidity.

When the entire population was evaluated, the most important finding was that neither the initially prescribed antimicrobial regimen nor its concordance was independently associated with mortality. Likewise, the association of β-lactams+macrolides is not better than the use of β-lactams alone in these patients. This finding would support the theory that treatment of CAP could be scaled down to monotherapy, once the pneumococcal aetiology had been ascertained, at least in patients with moderately severe disease. An encouraging nonsignificant trend stands out in reference to mortality when levofloxacin is used. Interestingly, in a randomised trial, FINCH *et al.* [25] found that patients treated with moxifloxacin had lower mortality and a shorter length of stay in hospital than those treated with a β-lactam, with or without a macrolide. It has also been recently reported that initial treatment with fluoroquinolones (levofloxacin 89.5%) is independently associated with a lower risk of treatment failure [26].

The current authors have also evaluated some clinically relevant situations (table 5), mainly in ICU patients and those with renal failure, chronic lung disease, bacteraemic pneumonia or PSI Class >III. In this latter case, the initial antimicrobial choice was associated with mortality. This means that in patients with PSI Class >III the choice of an antimicrobial regimen, other than β-lactam monotherapy, macrolide monotherapy, β-lactam+macrolide or levofloxacin alone or in combination, was associated with higher mortality. It is also remarkable that in bacteraemic patients, the choice of other combinations is close to the statistical significance regarding a major risk of mortality (HR 1.8, 95% CI 1–3.4, p=0.053; table 5). Finally, a subset analysis showed similar outcomes in patients with penicillin-susceptible *S. pneumoniae versus* those with penicillin-resistant isolates, except for the subgroup of patients with renal failure, in whom reduced susceptibility to penicillin was independently related to an increase in mortality (table 5). This is probably due to the more frequent use of antibiotics in these patients.

The lack of unique clinical features that accurately identify the specific pathogen, the increased antibiotic resistance, an unknown number of mixed infections and the great number of antibiotic choices, are some of the reasons that surround the debate. GLEASON *et al.* [8], showed that in almost 13,000 elderly in-patients with CAP, the initial therapy with a second-generation cephalosporin+macrolide, a nonpseudomonal third-generation cephalosporin+macrolide, or a fluoroquinolone alone, was independently associated with a lower 30-day mortality in patients hospitalised with pneumonia, than was therapy with a nonpseudomonal third-generation cephalosporin. The implications from these findings are that routine therapy against atypical pathogens may be important, even in elderly patients with CAP. In another population-based retrospective study [9], the inclusion of macrolides or fluoroquinolones in the initial empirical CAP therapy was also associated with improved survival, but this association varied from year to year, probably as a result of a temporal variation in the incidence of atypical pathogen. BROWN *et al.* [7] recently published another analysis of younger patients with CAP in which they demonstrated that the combination of ceftriaxone+macrolide was superior to other regimens, with respect to mean length of hospital stay and in-hospital mortality. However, this study raises the same questions as previous retrospective studies. For example, no information concerning the adequacy of diagnosis and therapy exists and only limited information regarding pathogens was available. Additionally, the authors did not assess the most sick-patient population, with severity of illness as one of the main factors that helps to select an initial antibiotic regimen. It is, therefore, interesting to note that a recently published, retrospective study, by WATERER *et al.* [11], which, with a design similar to the present study, concludes that adults with severe bacteraemic nonresistant CAP-SP have a significantly higher risk of death if they receive a single antibiotic rather than a combination of effective therapy. This supports the findings of other studies [12, 13], which found that dual antimicrobial therapy, including a macrolide, reduced mortality associated with bacteraemic CAP-SP. A recent study by BADDOUR *et al.* [16] reported that in critically ill patients with bacteraemic pneumococcal illness, combination therapy was associated with a lower 14-day mortality (23.4 *versus* 55.3%, p=0.0015), but this improvement in survival was independent on the class of antibiotics administered or the *in vitro* activity of the antibiotics prescribed. For noncritically ill patients, there was no difference in the 14-day mortality for patients treated with monotherapy *versus* combination. A number of possible explanations for the benefit of macrolides have been considered, such as antibiotic synergy, immunomodulatory effects and coverage of unrecognised atypical pathogens.

In spite of being the recommended regimen by a great number of guidelines for the management of CAP [27–29], theoretically, the combination of β-lactams+macrolides may be unwise, as the bacteriostatic agent may antagonise the effect of the bactericidal agent [15]. Some authors [30] have suggested that the combination of a macrolide and penicillin, if not synergistic, might at least not be antagonistic when the β-lactam agent is administered first, followed, some hours later, by the macrolide. Administration of multiple antimicrobials for CAP could also result in potentially more severe outcomes, in the form of increased drug-related adverse events. One-third of the current patients were explored for the possible coexistence of atypical pathogens, but only *Legionella* spp. and *C. pneumoniae* were both found in three patients, which might explain why regimens covering these organisms did not substantially affect the outcome in the current study. Moreover, evidence is lacking that clinical outcomes are improved by using antibiotics that are active against atypical pathogens, at least in nonsevere CAP [31, 32].

It is reasonable to assume that inadequate therapy of infection leads to an excess of mortality. Furthermore, risk of exposure to DAT is directly related to the possibility of being infected with a resistant pathogen. Specifically, receipt of DAT as result of infection with a resistant *S. pneumoniae* strain has been reported to be associated with a significantly higher mortality [4]. However, the current authors have not found DAT to be related to mortality, and only the loss of susceptibility to penicillin in patients with renal failure has been found to be

related. Current levels of penicillin resistance do not surpass MICs of 2 $\mu g \cdot mL^{-1}$ [17], and serum and pulmonary levels achieved with β-lactams are several times higher than these. Even full penicillin resistance strains may be successfully treated if large enough doses of penicillin, in frequent enough dosing intervals, are given. Therefore, only a few patients with penicillin-resistant pneumococcal CAP receive a true DAT. In the current series, a significant number of DATs were found among patients receiving macrolide monotherapy. Considering the high level of resistance to macrolides in the current patients, this finding could have clinical significance. However, most of the patients receiving this DAT had a less severe pneumonia (PSI Class I–III) and the exact role that antimicrobials play in the outcome of these patients is probably less critical. Overall, combination therapy was used more commonly in the more severe cases (possibly expected to have a higher mortality) and macrolide monotherapy was used in the less severe patients.

It has been recently reported by MENENDEZ *et al.* [33], that guideline-compliant therapy was strongly associated with improved survival. It is obvious that patients in the current series with a PSI Class >III, who had received antimicrobials classified as other combinations, did not follow the recommendations stated in the local guidelines. However, not all patients' characteristics can be conveniently classified and it is possible that when a physician encounters a severely ill patient, they will choose an unusual regimen of antibiotics, knowing beforehand that the patient will have an elevated risk of mortality [34]. What the present study indicates is that in patients with PSI Class >III, as well as other factors, such as shock, bilateral pneumonia and HIV infection, the antimicrobial choice may also be independently related to mortality. Finally, mortality rates of bacteraemic pneumococcal disease vary greatly between centres [35], suggesting that factors others than antibiotic therapy may also be important in the current study.

The present work has several limitations common to any observational study in which empirical antimicrobial regimen have not been selected at random. Clinicians' decisions to prescribe combinations of antibiotics are based on factors relevant to the individual patient [10, 36] and, consequently, many factors in addition to antibiotic therapy could have accounted for the present results. In fact, as the current authors have stated, initial antimicrobial choice is related to baseline severity of illness. The route, dose and duration of antibiotic therapy, the potential role of antibiotics taken prior to hospital admission, timing of the initial dose, consistent supportive care among centres (*e.g.* criteria for ICU admission) and history of pneumococcal vaccination may be additional confounding factors that have not sufficiently been addressed in this study [35, 37–41]. In contrast with other studies carried out in a very similar geographical area, but in just one hospital [13], which may contribute to the different findings observed, several recent prospective trials [25, 42] have not shown a benefit of combination therapy in CAP, although these trials were also flawed in some respects and again do not provide definitive answers. The present study adds to the controversy and in contrast to most large retrospective cohort studies, the patient population is well characterised, including severity of illness.

In conclusion, the current authors believe that the present evidence does not unequivocally support the use of any specific antibiotic agents or combinations in community-acquired pneumonia due to *Streptococcus pneumoniae* as long as this pathogen is rapidly and effectively covered. Randomised, prospective, blinded trials are needed to compare different antimicrobial regimens to demonstrate whether some of them offer true outcome advantages to community-acquired pneumonia patients.

ACKNOWLEDGEMENTS

The authors would like to thank F. Rodriguez-Salvanés and R. González-González of the Fundación de Investigación del Hospital de la Princesa (Madrid, Spain) for their invaluable assistance with the statistical analysis. Their contribution was extremely helpful and this manuscript would not have been possible without their generous effort.

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