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J. Rello
M. Catalán
E. Díaz
M. Bodí
B. Álvarez

Associations between empirical antimicrobial therapy at the hospital and mortality in patients with severe community-acquired pneumonia

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J. Rello (✉) · E. Díaz · M. Bodí
Critical Care Department,
University Hospital Joan XXIII,
Mallafré Guasch 4, 43007 Tarragona
e-mail: JRC@hj23.es
Tel.: +34-977-295818
Fax: +34-977-295878

M. Catalán
Critical Care Department,
University Hospital Doce de Octubre,
Madrid

B. Álvarez
Critical Care Department,
Hospital San Juan, Alicante, Spain

Abstract *Introduction:* The aim of the study was to examine different antibiotic choices and their relation to outcomes. *Methods:* We reviewed patients with severe community-acquired pneumonia (SCAP) from two multicenter studies. Empirical antimicrobial regimens were classified as: macrolides alone (group M); macrolides plus betalactams (group MB); macrolides plus betalactam/betalactamase inhibitor (group MBI); every regimen including aminoglycosides (group A); non-pseudomonal third-generation cephalosporins alone (group C); another betalactam alone (first- and second-generation cephalosporins, or betalactam/betalactamase inhibitor) (group B); fluoroquinolones (group F); and other regimens (group Misc). *Results:* Initial distribution of regimens was: group MB: 261 patients; group A: 65 patients; group C: 31 patients; group B: 23 patients; group M: 18 patients; group MBI: 13 patients; group F: 11 patients; group Misc: 38 patients. The lowest overall mortality was associated with initial treatment with a macrolide plus other agent (or alone). No deaths were documented among the 13 patients receiving amoxicillin/clavulanate plus a macrolide. The excess mortality for initial treatment with group A was significantly higher (14.2%; CI 95% 27.3–1.1) than the overall mortality rate between patients receiving a macrolide plus other agents. No significant differences were documented when mortality was adjusted for intubated patients. *Conclusion:* Clinicians select the empirical antibiotic regimen after classifying patients according to likely pathogens and prognosis. The inclusion of a macrolide as part of the initial therapeutic regi-men for SCAP appears to be as safe and effective as alternative options. Addition of a macrolide agent to a betalactam/betalactamase inhibitor or using a macrolide alone was a marker for less severe disease.

Keywords Severe community-acquired pneumonia · Antibiotic · Treatment · Macrolides

Introduction

Community-acquired pneumonia (CAP) is the most frequent cause of community-acquired infections admitted to the ICU. Because of the high mortality rate associated with pneumonia, it is essential that initial antimicrobial therapy is effective against the causative pathogen. Several national societies, including the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA), have published (and updated) guidelines for empirical antimicrobial therapy [1, 2, 3, 4]. The most important and controversial question now is to establish the optimal approach to patients with severe CAP.

From 1999 up to the present, at least four important studies examined the effect of the antibiotic regimen on the outcome of patients hospitalized with CAP. Stahl et al. [5] concluded that the use of macrolides as part of an initial therapeutic regimen appears to be associated with shorter LOS. Other recent papers [6, 7] suggested that patients with bacteremic pneumococcal CAP treated with a combination of a betalactam and a macrolide may have a better outcome. In another retrospective study, Gleason et al. [8] have reported a population-based study of Medicare patients who had been hospitalized with CAP in 1995 in the United States. They compared 30-day mortality for patients treated with CAP and observed that those treated with a betalactam/betalactamase inhibitor plus a macrolide presented significantly higher mortality. Similarly, inclusion of an aminoglycoside was associated with an increased risk of death. However, the combination of a betalactam plus an aminoglycoside has been shown to reduce mortality in patients with bacteremic *Klebsiella* spp pneumonia [9].

None of these studies included European patients, nor did they focus on subjects with severe CAP – the subpopulation in which the impact of the initial antibiotic choice on outcome is probably most critical. Both the IDSA and ATS guidelines [3, 4] recommended a specific and more aggressive approach, using combination therapy in this subset. However, even the authors of these guidelines warn against their use in clinical practice until the implications for patient outcomes are better understood [10].

In order to determine current prescribing practices in patients with SCAP requiring ICU admission, and to assess associations between empirical antimicrobial agents and patient outcomes, we designed a study with the following objectives: 1) to describe the empirical antimicrobial regimen most frequently prescribed for SCAP after hospital admission in Spain; and 2) to assess the associations between empirical antibiotic regimens, some indicators of severity (APACHE II, intubation, shock), and ICU mortality. Our primary hypothesis was that a combination of a macrolide plus a betalactam would be associated with different outcome, based on prior references [5, 6, 7]. Specifically, we sought to confirm the results of the study by Gleason et al. [8] and to determine whether the association of a macrolide plus a betalactam/betalactamase inhibitor was associated with increased mortality.

Methods

We performed a retrospective case analysis based on data from two national databases which were designed and described elsewhere [11, 12] for other purposes. Subjects were all patients aged 18 years or older admitted to the ICU with a diagnosis of severe CAP. Patients from nursing homes were not considered eligible for study. The first database [11] covers the period 1991–1992 and the second [12] the period 1993–1999. No cases were duplicated because the study period was different.

For the diagnosis of CAP to be accepted, patients had to present acute illness (<10 days of symptoms), a new chest radiographic infiltrate confirmed by a radiologist, and clinical signs suggesting acute pneumonia including fever, hypothermia, cough, sputum production, dyspnea, pleuritic pain, clinical evidence of lung consolidation or an alteration in the white cell count. These criteria are consistent with published guidelines for CAP diagnosis [4]. Severe CAP was diagnosed with the same criteria used in Rello et al. [11].

Exclusion criteria included neutropenia (<500 cells/mm^3), and transplantation or identification of viral etiology. We also excluded subjects who did not receive a dose of antibiotic agents between the first 24 h after presentation or any subject whose basic data were lacking.

Basic demographic data, antibiotic treatment, and culture results were recorded for all patients included. No information on "in vitro" sensitivities was recorded. Other more specific variables, such as duration of antibiotic exposition, evaluation as inadequate choices, specific severity scores for CAP, initial pO_2 and pH, or radiographic appearance were not recorded. Empirical antibiotic therapy was defined as any antibiotic therapy administered within the first 24 h after presentation at hospital. Outcome measures included ICU mortality and ICU length of stay (LOS).

Associations between patient outcomes and initial antibiotic regimens were assessed by stratification according to similarity of the regimen. Group MB used therapy with a macrolide alone or in combination with a betalactam. Combination of a macrolide plus a betalactam/betalactamase inhibitor was categorized as group MBI. Group M comprised patients receiving a macrolide alone. Group A comprised regimens that included an aminoglycoside. Group B comprised patients receiving a betalactam alone, except for patients receiving a non-pseudomonal third-generation cephalosporin alone, who were classified as group C. Patients receiving a fluoroquinolone were classified as group F. Finally, all patients with an overlap or a miscellaneous choice not consistent with prior groups were arbitrarily grouped as group Misc.

Univariate analysis was performed with the CIA software. Mortality rates are expressed as differences between means [95% confidence intervals (CI)]. $P<0.05$ was considered statistically significant.

Results

Four hundred and sixty patients met the inclusion criteria for analysis. A further 11 cases of SCAP were identified but were excluded because data analysis was incomplete or because the origin was viral. Thus, 1.1% of the overall ICU admissions in the ICU over the study period were included. The basic demographic information is summarized in Table 1. Distribution of respiratory and renal failures were enclosed. Overall ICU mortality was 30%. Median APACHE II at admission was 20. The most frequent pathogens were *Streptococcus pneumoniae* (15%) and *Legionella pneumophila* (5.6%). Thirty-five episodes were polymicrobial. Certain patients (11%) were coded as having bacteremia and 42.6% an unknown etiology. Others (34.3%) received prior antibiotic therapy before hospital admission.

The most common prescribed regimen was a macrolide in combination with a betalactam (group MB): ceftazidime (15 patients, five deaths), second-generation cephalosporin (11 patients, two deaths), and ceftriaxone or cefotaxime (235 patients, 64 deaths). The combination

Table 1 Demographics and main baseline characteristics of the study population

Variable	Overall	Group 91–92	Group 93–94
Median age (mean±SD in years)	59.1±18.0	56.4±17.6	61.8±19.1
Gender: male	349	190	159
COPD	159	74	85
Alcoholism	113	90	23
Solid neoplasia	31	20	11
Cardiomyopathy	52	27	25
Diabetes	55	40	15
Positive blood cultures	51	11	40
Mortality within first 2 days	65	35	30
APACHE II (median)	20	20	19
S. pneumoniae	69	30	41
L. pneumophila	26	21	5
Haemophilus influenzae	15	10	5
Pseudomonas aeruginosa	11	3	8
Prior antibiotic exposure	158	85	73
Acute renal failure	111	94	17
ARDS	163	142	21
Multiorgan dysfunction	78	67	11

Table 2 Use of initial antibiotic regimens and indicators of severity in 460 patients with SCAP. (*Group MB* antimicrobial regimen which included a macrolide plus a betalactam, *group A* antimicrobial regimen which included an aminoglycoside, *group B* antimicrobial regimen based on a betalactam alone, *group C* patients receiving a non-*Pseudomonal* third-generation cephalosporin alone, *group F* antimicrobial regimen which included a fluoroquinolone, *group M* antimicrobial regimen based on a macrolide alone, *group MBI* patients receiving a macrolide plus a betalactamic/betalactamase inhibitor, *group Misc* all other regimens)

Initial antimicrobial regimen	Prevalence	APACHE II	Intubated	Shock
Group MB	261 (56.7)	19.8±6.2	149 (57.0)	64 (24.1)
Group A	65 (14.3)	21.1±7.3	54 (83.0)*	37 (56.9)*
Group C	31 (6.7)	18.5±8.2	24 (77.4)*	10 (32.2)
Group B	23 (5.0)	22.8±6.1	16 (69.5)	8 (34.7)
Group M	18 (3.9)	19.6±7.6	13 (72.2)	3 (16.6)
Group MBI	13 (2.8)	19.1±8.3	6 (46.1)	0
Group F	11 (2.3)	20.1±6.3	10 (90.9)*	5 (45.4)
Group Misc	38 (8.2)	18.8±9.0	35 (92.1)*	12 (31.5)
Total	460 (100)	21.0±6.0	307 (66.7)	139 (30.2)

of a macrolide plus a betalactam/betalactamase inhibitor (group MBI) was prescribed in 13 patients (no deaths). A macrolide alone (group M) was given to 18 patients (two deaths). Thus, mortality was 18.1% (2/18) for patients receiving a macrolide alone, and 27.2% (64/235) for those receiving combination with a betalactam (P>0.20). The subgroup receiving a macrolide plus ceftazidime had a mortality of 33.3%. No deaths were documented in the 13 patients receiving amoxicillin/clavulanate plus a macrolide. Details on distribution of shock, intubation, and APACHE II are shown in Table 2.

The second most commonly prescribed group included an aminoglycoside alone (15 patients, nine deaths) or in combination (50 patients, 17 deaths) (group A). Therapy enclosing an aminoglycoside was associated with a significant higher proportion of acute renal failure when compared with the group MB (36.9% vs 19.8%, P value <0.05). The APACHE II score at admission was 21.1±7.3 (median 21), and it was not significantly higher when compared with group MB (see Table 2). However, a significantly higher proportion of patients (P value <0.05) underwent intubation or required vasopressors, when compared with group MB.

The third most frequently prescribed group was group C, a non-pseudomonal third-generation cephalosporin alone (31 patients, 11 deaths). Group B constituted by other betalactams (first-generation cephalosporin, six patients; second-generation cephalosporins, nine patients; or betalactam/betalactamase inhibitor, eight patients) alone was prescribed as initial therapy to 23 patients (six deaths). Group F comprised 11 patients (three deaths) who received a fluoroquinolone as monotherapy or in combination. Ciprofloxacin was the quinolone chosen in all these cases for atypical organism coverage. Finally, 38 patients constituted a miscellaneous group (group Misc) including all other regimens. Groups C, F, and Misc also had a higher proportion of patients who underwent intubation, compared with group MB (Table 2).

Subgroup analysis for mortality and median ICU LOS is detailed in Table 3. The excess mortality for initial

Table 3 Use of initial antibiotic regimens and outcome in patients with SCAP. (*Group M* antimicrobial regimen which included a macrolide alone, *group A* antimicrobial regimen which included an aminoglycoside, *group B* antimicrobial regimen based on a betalactam alone,*group C* patients receiving a non-*Pseudomonal* third-generation cephalosporin alone, *group F* antimicrobial regimen which included a fluoroquinolone, *group MBI* patients receiving a macrolide plus a betalactamic/betalactamase inhibitor, *group MB* antimicrobial regimen which included a macrolide plus a betalactam, *group Misc* all other regimens, *LOS* median ICU Length of stay; days)

Initial antimicrobial	Overall ICU mortality	ICU Mortality in intubated patients	LOS
Group Misc	44.7%*	48.6%	5
Group A	40.0%*	48.1%	39
Group C	35.5%	45.8%	7
Group MB	27.2%	40.4%	17
Group F	27.2%	30.0%	21
Group B	26.7%	37.5%	15
Group M	11.1%	15.3%	16
Group MBI	0	0	6

treatment with an aminoglycoside (alone or plus any other agent) was significantly higher (14.2%; CI 95% 27.3–1.1) than the overall mortality rate between patients receiving a macrolide in combination with other agents (25.8%).Since antibiotic therapy would be expected to have little influence on early deaths, we reanalyzed mortality for subgroups after excluding all deaths that occurred within 48 h of ICU admission. Although the reduction in the study group (n=395) meant that no statistically significant differences could be obtained, we obtained similar trends of mortality (data not shown). However, no significant differences between the different prescription groups were documented when ICU mortality was reanalyzed in the subgroup of intubated patients (Table 3).

Additionally, the analysis of mortality associated with monotherapy or combination therapy was evaluated and no difference was found (27.2% vs 31.6%, respectively; P=NS). Anti-pseudomonal coverage was also assessed and no significant difference in mortality was found (31.7% vs 31.5%, P=NS): Finally, the reduction in mortality for regimens including activity against *Legionella* or other atypical pathogens was not significant (22.5% vs 25.7%, P=NS).

Discussion

To our knowledge, this is the first study to explore associations of antibiotics and mortality rates in patients hospitalized in the ICU for severe CAP. The most frequently prescribed empirical regimen (56.7% of cases) included a combination of a betalactam with an intravenous macrolide, and it was associated with 27.2% mortality. In contrast, overall mortality and development of acute renal failure in patients receiving therapy with an aminoglycoside was significantly higher, an observation that may raise concern about the use of this regimen. Our findings add information to that presented by Gleason et al. [8], and suggest that the combination of a macrolide plus a betalactam/betalactamase inhibitor does not have worse outcome. On the other hand, our findings suggest that clinicians selected the empirical antibiotic regimen after classifying patients according to likely pathogens and prognosis.

Our findings suggest that antimicrobial regimens which include a macrolide in combination are as safe and effective as alternative options. There are many possible explanations for this. Most patients received a macrolide plus non-pseudomonal third-generation cephalosporins, a regimen which is in agreement with the recommendations of several expert panels in the past decade, such as the 1998 IDSA guidelines [1] and the 1993 ATS guidelines [2]. In addition to a direct antimicrobial effect, especially against *Legionella* and other atypical pathogens, and the potential benefit of synergy when used in combination, there is some evidence that macrolides may reduce the proinflammatory effects of various bacterial products [6].

An alternative explanation for the apparent benefit of using a regimen including a macrolide is that this therapy was used preferentially for patients in the lower severity strata, despite the fact that no significant difference was obtained when APACHE II at admission was compared between the initial antibiotic regimens (Table 2). However, specific scores for patients with community-acquired pneumonia were not tested. Indeed, despite the APACHE II score at admission not being significantly different between groups, groups with macrolides had the lowest incidence of patients who underwent intubation or vasopressors. When mortality was reanalyzed in the subgroup of intubated patients, no significant differences in mortality were documented.

In contrast with Gleason's report [8], betalactamase inhibitors/betalactamic agents with macrolides were not associated with a poorer outcome in our study. In Gleason's study [8], this combination was prescribed in only 1.2% of patients in risk class V according to Fine's classification [13]. Gleason et al. [8] emphasized that patients treated with betalactamic/betalactamase inhibitors

alone over the 48 h after admission presented an adequate clinical response; they suggested the addition of a macrolide to the initial therapy may be reflecting a bias by enclosing those with a suboptimal clinical response. A recent study [14] in a group of Medicare beneficiaries aged 65 years, who were hospitalized with CAP in ten Western States in the USA, concluded that a macrolide/betalactam combination therapy was associated with a significantly reduced mortality rate when compared with betalactam monotherapy or other antibiotic regimens. Similarly, therapy with a betalactam/betalactamase inhibitor combination accounted for 1% of regimens and they documented yearly variability in the benefit from such therapy.

This is an observational study involving a large number of ICUs over a decade and the prescribing option was left to the discretion of the attending physician. As a consequence, several of the options (such as aminoglycosides or macrolides alone, betalactams alone or a combination of cefuroxime/ceftazidime plus a macrolide) are regarded as suboptimal by the authors [15]. Our findings suggest that educational measures are warranted to eliminate some of these prescriptions in a country with high incidence of penicillin-resistant *S. pneumoniae* and *L. pneumophila.*

Our study has both strengths and potential limitations. The strengths of our study include the use of national multicenter databases which provide information over a long period of time. Thus, local annual variation in the incidence of *Legionella,* or epidemics caused by *C. pneumoniae* are not expected to influence the current study. Our sample size is relatively large, allowing the identification of infrequent associations that may be clinically significant. In spite of this, our ability to assess macrolide monotherapy or regimens containing fluoroquinolones were limited by the small number of patients who received those agents. Finally, most published reports of pneumonia are for short periods or involve relatively few patients at a small number of hospitals. The fact that we identified cases of SCAP at a variety of institutions using a wide spectrum of practices and therapies gives the study a far broader scope than such carried out in a single institution or in a limited region.

Because of the retrospective nature of the analysis, however, care must be taken not to overinterpret these findings. Admission criteria were not standardized, some antibiotic options were suboptimal, and no specific scores for pneumonia were measured. Thus, these data may have varied from institution to institution. Increasing antibiotic resistance might affect the benefit of macrolide treatment, but no information was available on bacterial resistances in the current study. Since both pathogens and patterns of sensitivity present geographical variations, these findings may not necessarily be reproducible in other countries. Obviously, prescription patterns also may be substantially different in other countries and in the future. Most of the cases included in the study were recorded before urinary antigen detection tests became available, and testing for atypical pathogens in clinical practice might alter the prescription regimens. Similarly, newer fluoroquinolones with enhanced activity against *S. pneumoniae* appeared before the end of the study period, although they are not currently licensed for patients with severe episodes. All these drawbacks may affect the generalizability of the findings. Similarly, different end-points for mortality may have been used, although it is unlikely that this would have affected the final outcome.

More importantly, a multivariate analysis controlling for severity scores, intubation, and shock would be optimal due to the observed imbalance between groups. Unfortunately, the tested group (MBI), and several others, include less than 10% of the study population precluding such an analysis due to the lack of stability of the resulting models. As acknowledged by an editorial comment by Dowell [16], even the information available on a retrospective study combined with standard adjustment techniques can only partially adjust for some biases. However, in the absence of treatment efficacy data from extremely large and technically difficult trials, our study provides some information which would be useful as an opportunity to improve the empirical antibiotic regimen prescribed to hospitalized patients with severe community-acquired pneumonia.

In summary, despite the above limitations, this study is the first to compare outcomes with initial antibiotic prescriptions in the largest series of patients with severe community-acquired pneumonia. It provides potentially important data for improving outcome in this population. Our findings corroborate reports that regimens including aminoglycosides may be suboptimal for patients with SCAP. The current study suggests that a treatment for SCAP based on the use of macrolides as part of the initial therapeutic regimen is the most frequent option in Spain, i.e., macrolides plus betalactam/betalactamase inhibitor which is as safe and effective as alternative options.

Finally, the findings of our study and the study reported by Gleason [8] suggest that clinicians select the empirical antibiotic regimen in a patient-based policy rather than following general guidelines. They used multiple options, and the decision procedure may be improved using educational programs to change physicians' culture. In spite of our discrepancies, we agree with Gleason [8] that in the future, randomized trials are warranted to confirm which is the optimal option before the adoption of new strategies (such as newer fluoroquinolones) for therapy of community-acquired pneumonia in critically ill patients.

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