

# Usefulness of Betalactam Therapy for Community-Acquired Pneumonia in the Era of Drug-Resistant *Streptococcus pneumoniae*: A Randomized Study of Amoxicillin-Clavulanate and Ceftriaxone

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## ABSTRACT

Empirical antibiotic therapy of community-acquired pneumonia (CAP) has been complicated by the worldwide emergence of penicillin resistance among *Streptococcus pneumoniae*. The impact of this resistance on the outcome of patients hospitalized for CAP, empirically treated with betalactams, has not been evaluated in a randomized study. We conducted a prospective, randomized trial to assess the efficacy of amoxicillin-clavulanate (2 g/200 mg/8 hr) and ceftriaxone (1 g/24 hr) in a cohort of patients hospitalized for moderate-to-severe CAP. Three-hundred seventy-eight patients were randomized to receive amoxicillin-clavulanate (184 patients) or ceftriaxone (194 patients). Efficacy was assessed on Day 2, after completion of therapy and at long term follow-up. There were no significant differences in outcomes between treatment groups, both in intention-to-treat and per-protocol analysis. Overall mortality was 10.3% for amoxicillin-clavulanate and 8.8% for ceftriaxone (NS). There were 116 evaluable patients with proven pneumococcal pneumonia. Rates of high-level penicillin resistance (MIC of penicillin  $\geq 2$   $\mu\text{g/mL}$ ) were similar in the two groups (8.2 and 10.2%). Clinical efficacy at the end of therapy was 90.6% for amoxicillin-clavulanate and 88.9% for ceftriaxone (95% C.I. of the difference:  $-9.3$  to  $+12.7\%$ ). No differences in outcomes were attributable to differences in penicillin susceptibility of pneumococcal strains. Sequential i.v./oral amoxicillin-clavulanate and parenteral ceftriaxone were equally safe and effective for the empirical treatment of acute bacterial pneumonia, including penicillin and cephalosporin-resistant pneumococcal pneumonia. The use of appropriate betalactams in patients with pneumococcal pneumonia and in the overall CAP population, is reliable at the current level of resistance.

## INTRODUCTION

EMPIRICAL ANTIBIOTIC THERAPY of community-acquired pneumonia (CAP) is a controversial medical topic today.<sup>3,14</sup> This is largely due to the worldwide emergence of antibiotic resistance among *Streptococcus pneumoniae*, which remains the most frequent cause of CAP requiring hospitalization.<sup>2,7,25</sup> One of the main issues regarding CAP therapy is whether or not betalactams can be used successfully against betalactam-resistant pneumococci. In a previous, nonrandomized study, we have shown that intravenous high-dose penicillin and some expanded-spectrum cephalosporins were effective for the treatment of pneumococcal pneumonia caused by strains with minimal inhibitory concentrations (MICs) up to 2  $\mu\text{g/mL}$ .<sup>29</sup>

However, the MICs of penicillins and cephalosporins above which therapeutic failures would be expected are not known.<sup>18</sup> In addition, the impact of penicillin resistance on the outcome of a large cohort of patients with CAP receiving empirical betalactam therapy has not been evaluated prospectively. Most authorities do recommend third-generation cephalosporins or betalactam-betalactamase inhibitors as the first line therapy for hospitalized CAP, but suggest the use of alternative drugs such as vancomycin or fluoroquinolones for strains resistant to penicillin (MIC  $\geq 2$   $\mu\text{g/mL}$ ), or as empirical therapy in critically ill patients; however these suggestions are based on 'in vitro' data, and firm recommendations must await additional controlled studies.<sup>1,3,16,32</sup>

To address these issues in an area with high prevalence of

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antibiotic-resistant pneumococci, we performed a randomized trial, comparing two commonly used betalactam agents in the treatment of moderate-to-severe CAP: amoxicillin-clavulanate and ceftriaxone. MICs of both antibiotics against resistant pneumococci are usually lower than that of penicillin G and their broad-spectrum makes them safe enough for empirical therapy of CAP of presumed bacterial etiology.<sup>23,33</sup>

## PATIENTS AND METHODS

### Study design

The design was conducted at Bellvitge Hospital, a 1000-bed University hospital in Barcelona, Spain, which serves an area of 1,100,000 inhabitants. It was comparative, prospective, randomized, and assessor-blinded in early assessments. All patients included gave informed consent to enter, and the study was approved by the Ethical Committee at our institution.

### Patient eligibility

All nonimmunosuppressed adult patients with moderate-to-severe CAP who were admitted to the hospital from February 1995 through May 1997 were considered for study inclusion. Patients were excluded if they met one or more of the following criteria: unwillingness to enter the study; age  $\leq 16$  years; hypersensitivity to  $\beta$ -lactam antibiotics; pregnancy or breastfeeding; immunosuppression (AIDS, end-stage neoplasia, cytotoxic therapy, absolute neutropenia, or transplantation); shock unresponsive to therapy; concomitant endocarditis or meningitis; high clinical suspicion of *Legionella*, atypical, viral or aspiration pneumonia; previous antibiotic therapy for more than 24 h; and previous hospitalization within the past 14 days.

### Randomization

Eligible patients were randomized by the infectious disease consultant, who opened sealed, sequentially numbered envelopes. Random blocks of 25 allocations equally divided between regimens were used. Patients were assigned to receive either i.v. amoxicillin-clavulanate (2 g/200 mg every 8 hr) or i.v. ceftriaxone (1 g every 24 hr) for at least 72 hr. After a significant clinical improvement was achieved, sequential oral amoxicillin-clavulanate (1 g/125 mg every 8 hr) or i.m. ceftriaxone (1 g every 24 hr) were initiated. The addition of intravenous erythromycin at randomization was allowed if indicated by the attending physician. No other antibiotic therapy was permitted during the study period. All medication was provided by the hospital pharmacy.

### Definitions

CAP was defined as an acute respiratory illness associated with one or more of the following: fever or hypothermia, cough, sputum production, pleuritic chest pain, dyspnea, altered breath sounds on auscultation; plus the presence of a new infiltrate on a chest radiograph. CAP was considered moderate-to-severe when one or more of the following criteria was present: age  $\geq 70$  years;  $\text{PaO}_2 < 60$  mmHg or  $\text{PaO}_2/\text{FiO}_2 < 300$ ; multilobar

radiological involvement; hypotension or shock; and underlying disease such as alcoholism, chronic obstructive pulmonary disease (COPD), congestive heart failure, renal failure, splenectomy and diabetes mellitus. The simplified acute physiology score (SAPS) was applied as described elsewhere.<sup>19</sup> To stratify patients in risk classes we used the validated prediction rule calculated according to the Pneumonia Severity Index (PSI) scores, developed by the Pneumonia Outcomes Research Team as described elsewhere.<sup>11</sup> Overall mortality was defined as death by any cause within 30 days of hospitalization.

Etiological diagnosis of CAP was considered definitive when there was: isolation of a respiratory pathogen from a normally sterile specimen; isolation of *L. pneumophila* or *Mycobacterium tuberculosis* from sputum; detection of pneumococcal antigens by latex agglutination or pneumococcal DNA by polymerase chain reaction (PCR) in pleural fluid or transthoracic needle aspiration (TNA) specimens; detection of *L. pneumophila* serogroup 1 antigen in urine; four-fold increase in the antibody titre or seroconversion for *Mycoplasma pneumoniae*, *Chlamydia psittaci*, *Chlamydia pneumoniae*, *Coxiella burnetii*, *L. pneumophila*, respiratory syncytial virus, influenza A virus and parainfluenza 3 virus. Etiological diagnosis was considered presumptive when a predominant microorganism that correlated with a predominant morphotype in the Gram stain was isolated from sputum samples of good quality [presence of  $>25$  polymorphonuclear leukocytes and  $<10$  squamous cells per low-magnification field ( $\times 10$ )]. Presumptive aspiration pneumonia (anaerobic infection) was diagnosed on a clinical and radiological basis, in patients with specific risk factors. The remaining cases were considered as pneumonia of unknown etiology.

### Clinical and bacteriological evaluation

At the initial visit and before starting antibiotic therapy, each patient underwent a complete history and physical examination. Chest radiographs, arterial blood gas determinations, and basic chemistry and hematology tests were performed. Two sets of blood cultures were drawn and a sputum sample was processed for Gram stain and culture if available. Invasive procedures such as bronchoscopy or TNA were performed if indicated by the attending physician.

Follow-up visits were performed daily during hospital stay. Chest radiographs, hematology and chemistry tests, and repeated sputum cultures, if obtainable, were performed on Day 2, at the end of study and at the long-term follow-up visit, approximately 1 month after discharge. Blood cultures were repeated at 48 hr if initially positive, and when clinically indicated.

### Microbiological studies

Investigation of pathogens in blood, normally sterile fluids, sputum and TNA samples and serological studies were performed by standard microbiological procedures. Latex agglutination and PCR detection of *S. pneumoniae* was performed in TNA samples as described elsewhere.<sup>13</sup> Detection of *L. pneumophila* serogroup I antigen in urine was performed by an immunoenzymatic commercial method (Legionella Urinary Antigen, Binax, Portland, ME).

Susceptibility tests in *H. influenzae* strains were performed by a microdilution method with *Haemophilus* test medium, as described in NCCLS standards.<sup>27</sup> Detection of betalactamase production was performed by using a commercial chromogenic cephalosporin test (Nitrocef; Cefinase; Becton Dickinson Microbiology Systems, Cockeysville, MD).

Susceptibility tests of *S. pneumoniae* strains were performed by a microdilution method with Mueller–Hinton broth (Ca<sup>++</sup> and Mg<sup>++</sup> cation-adjusted) supplemented with 5% lysed horse blood, as described in NCCLS standards.<sup>27</sup> The antibiotics tested were: penicillin, amoxicillin-clavulanate, ceftriaxone, erythromycin, clindamycin, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole. MIC was defined as the lowest concentration of antimicrobial that prevented visible growth after an overnight incubation of plates at 35°C. Resistance to antimicrobial agents was defined according to the NCCLS criteria.<sup>26</sup> Serotyping of pneumococcal strains was performed at the Spanish Pneumococcal Reference Laboratory (Majadahonda, Madrid) by detecting the quellung reaction with use of 46 antisera provided by the Staten Serum Institut (Copenhagen).

### Assessment of efficacy

Clinical efficacy was assessed three times during follow-up. The first evaluation, "early assessment," took place on Day 2. Two experienced clinical investigators (F.M. and F.G., in most cases), who were blind to the treatment regimen, classified the response as: (1) improvement, when the acute symptoms had clearly regressed; (2) failure, in any of the following circumstances: no apparent clinical response to therapy, septic metastases, previously unrecognized shock or hemodynamic failure, worsening of respiratory failure, radiological progression, or severe adverse events; and (3) indeterminate, when improvement was insufficient. In these cases, a new clinical evaluation was performed 24 hr later and the case was definitively classified as failure or improvement.

The second evaluation, "end of therapy assessment," was performed 24–48 hr after completion of therapy. Cases were classified as: (1) cure, when clinical findings of pneumonia had disappeared and there was radiological improvement; (2) failure, under the following circumstances: lack of improvement, superinfection, inability to complete treatment due to adverse events, or death by any cause.

The third evaluation, "final assessment," was performed at the long-term follow-up visit. Cases were classified as: (1) cure, when there was clinical and radiological resolution; (2) failure, when there was persistence or recrudescence of symptoms, or any case previously classified as failure; and (3) unevaluable per protocol analysis, when a noninfectious cause of pulmonary infiltrates was documented, or if patients did not attend the follow-up visit. Assessment of health status of all patients not attending the visit was attempted by telephone contact.

Only culture-positive pneumonias were considered for bacteriological evaluation, which was performed three times during follow-up: at 48 hr of therapy, after completion of treatment, and at the long-term follow-up visit. Response was classified as satisfactory if there was eradication of the microorganism or if respiratory samples could not be obtained due

to improvement; unsatisfactory, if the previously identified pathogen was still isolated, or when superinfection requiring additional antimicrobial therapy occurred; and indeterminate, when the evaluation could not be performed for any reason.

### Statistical analysis

The trial was designed under the hypothesis that clinical cure rate would be equivalent in the treatment groups. The sample size was determined in order to detect a 15% difference in the clinical cure rate for pneumococcal pneumonia, if the expected clinical cure rate using parenteral ceftriaxone in patients with moderate-to-severe pneumococcal pneumonia was 80%. With a power of 80% [type II error ( $\beta$ ) = 0.20] and using a two-sided 95% confidence interval [type I error ( $\alpha$ ) = 0.05], 75 evaluable patients per treatment group were required. Considering that *S. pneumoniae* would cause around 50% of moderate-to-severe bacterial CAP, and allowing for 15% unevaluability, a total of 345 patients was needed.

Comparisons between groups were performed by a  $\chi^2$  test with continuity correction or an independent sample *t*-test, when appropriate. Significance was defined at a *P* value < 0.05 using a two-sided test.

For assessment of clinical efficacy, two analyses were performed: an intention-to-treat analysis, including all randomized patients, and a per protocol analysis of all evaluable patients. Special emphasis was placed on the assessment of response in proven pneumococcal pneumonia, with subanalysis of penicillin-resistant cases. A two-sided 95% confidence interval was calculated for the difference in success rates between the two treatment groups.

## RESULTS

### Trial profile

Of the 543 patients who were considered for inclusion during the study period, 378 were finally randomized to receive amoxicillin-clavulanate (184 patients) or ceftriaxone (194 patients) and analyzed by intention-to-treat. After excluding 55 additional unevaluable patients, the remaining 323 were considered evaluable and analyzed per protocol. Figure 1 illustrates the trial profile. We kept a book log with the diagnosis and outcome of all nonrandomized patients.

### Characteristics of patients

Table 1 shows the baseline characteristics of the 378 randomized patients. There were no differences between treatment groups, including the distribution of most significant underlying diseases, such as cancer, COPD, chronic heart disease, and diabetes mellitus. Baseline characteristics of the 323 evaluable patients and the 115 patients with proven pneumococcal pneumonia were also similar.

### Etiology

Table 2 shows the distribution of causative organisms of the 323 evaluable cases, in both treatment groups. In 83 (52.9%) pneumonias of the amoxicillin-clavulanate group and 86

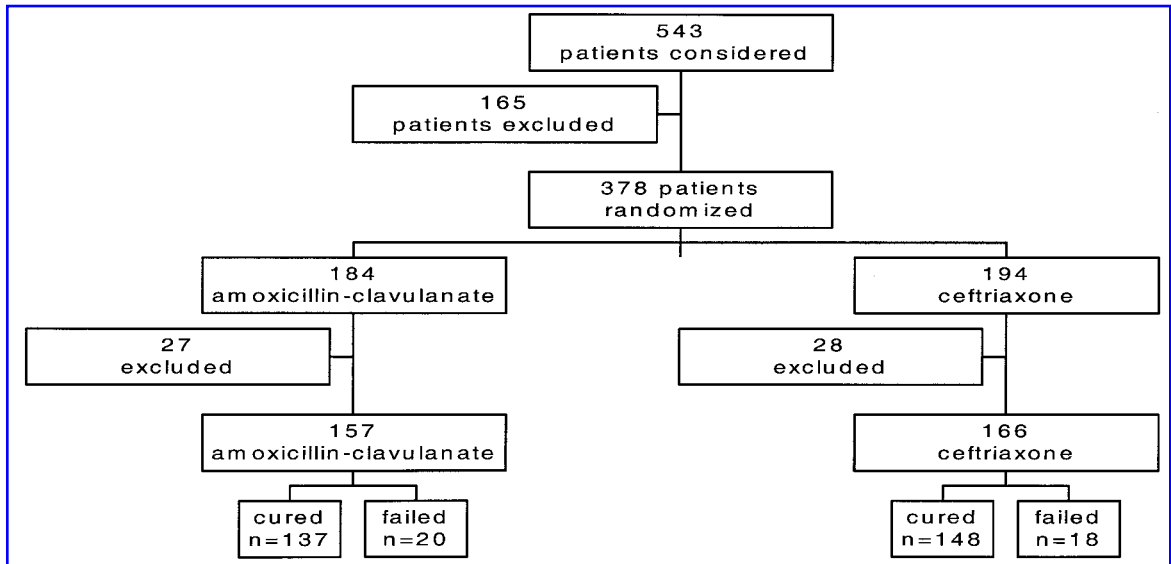


FIG. 1. Trial profile.

(51.8%) of the ceftriaxone group no pathogens were identified. Overall, *S. pneumoniae* was the most frequently identified causative agent, accounting for 71.6 and 78.7% of pneumonias with a proven etiology respectively, and 34.9% of the total illnesses included in the study.

#### Antibiotic therapy

Mean duration of i.v. therapy was 5.4 days for the amoxicillin-clavulanate group and 5.3 days for the ceftriaxone group ( $p = 0.63$ ). Complete duration of antibiotic therapy was 10.9 days and 10.1 days, respectively ( $p = 0.18$ ). Seventeen patients (9.2%) in the amoxicillin-clavulanate group and 25 patients

(12.9%) in the ceftriaxone group initially received combination erythromycin therapy. Seven patients with proven pneumococcal pneumonia (2 and 5, respectively) received combination therapy with erythromycin. In five of them the diagnosis was performed by isolation of *S. pneumoniae*. Four of these strains were fully sensitive to penicillin (MIC < 0.03  $\mu\text{g/mL}$ ) and the remaining had an MIC of 2  $\mu\text{g/mL}$ .

#### Intention-to-treat analysis

Patients were hospitalized for a mean of 10.7 days in the amoxicillin-clavulanate group and 11.3 days in the ceftriaxone group. Fourteen patients in each group required intensive care

TABLE 1. BASELINE CHARACTERISTICS OF ALL RANDOMIZED PATIENTS

| Characteristic                           | Amoxicillin-clavulanate<br>No. (%) | Ceftriaxone<br>No. (%) |
|--|------------------------------------|------------------------|
| Patients                                 | 184                                | 194                    |
| Age, y (mean)                            | 66                                 | 67                     |
| Sex (male/female)                        | 123/61                             | 144/50                 |
| Underlying disease                       | 130 (70.7)                         | 147 (75.8)             |
| Previous antibiotic therapy              | 35 (19.0)                          | 35 (18.0)              |
| Influenza vaccine                        | 75 (40.8)                          | 96 (49.5)              |
| Pneumococcal vaccine                     | 10 (5.4)                           | 5 (2.6)                |
| Impaired consciousness                   | 19 (10.3)                          | 26 (13.4)              |
| Multilobar infiltrate                    | 52 (28.3)                          | 62 (32.0)              |
| Shock at onset                           | 7 (3.8)                            | 5 (2.5)                |
| PSI classes (IV-V)                       | 110 (59.8)                         | 113 (58.2)             |
| SAPS (mean)                              | 9.4                                | 9.4                    |
| Axillary temperature (mean) °C           | 38.2                               | 38.2                   |
| Respiratory rate per min (mean)          | 29                                 | 30                     |
| PO <sub>2</sub> /FiO <sub>2</sub> (mean) | 274                                | 270                    |
| Empyema                                  | 10 (5.4)                           | 11 (5.7)               |
| Bacteremia                               | 20 (10.9)                          | 26 (13.4)              |

No differences were statistically significant. SAPS, Simplified acute physiology score; and PSI, pneumonia severity index.

TABLE 2. DISTRIBUTION OF CAUSATIVE AGENTS IN 323 EVALUABLE PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA ACCORDING TO TREATMENT GROUPS

| <i>Causative agents<sup>a</sup></i> | <i>Amoxicillin-clavulanate</i> | <i>Ceftriaxone</i> |
|-------------------------------------|--------------------------------|--------------------|
| Patients                            | 157                            | 166                |
| <i>Streptococcus pneumoniae</i>     | 53                             | 63                 |
| <i>Haemophilus influenzae</i>       | 15                             | 13                 |
| <i>Moraxella catarrhalis</i>        | 3                              | 3                  |
| <i>Enterobacteriaceae</i>           | 1                              | 3                  |
| Others                              | 5                              | 1                  |
| Atypical agents <sup>b</sup>        | 4                              | 5                  |
| No pathogen identified              | 83 (52.9%)                     | 86 (51.8%)         |

<sup>a</sup>The sum is more than 323 because fifteen patients had mixed infections (7 in amoxicillin-clavulanate group and 8 in ceftriaxone group).

<sup>b</sup>All of these patients had mixed infections.

unit (ICU) admission and most of them underwent mechanical ventilation (10 and 10). In-hospital complications were observed in 51 (27.7%) and 54 (27.8%) patients, respectively, the most frequent being congestive heart failure (10 and 9), and pleural empyema (10 and 11).

As shown in Table 3, there were no significant differences in clinical efficacy between the two treatment groups in any of the three assessments. In the final assessment, the success rates were 73.9 and 74.2%, respectively. Overall mortality was similar among patients receiving amoxicillin-clavulanate (10.3%) and those receiving ceftriaxone (8.8%).

Both drugs were well tolerated, and most adverse events were mild; only two patients stopped treatment due to adverse events. Forty-one patients (22.2%) in the amoxicillin-clavulanate group and 34 patients (17.5%) in the ceftriaxone group presented drug-related adverse events, the most frequent being phlebitis (30 and 25) and gastrointestinal discomfort (9 and 2).

#### *Patients excluded after randomization*

Fifty-five patients were excluded from the per protocol analysis, 27 in the amoxicillin-clavulanate group and 28 in the ceftriaxone group. Most had noninfectious pulmonary infiltrates or atypical or *Legionella* pneumonia. Table 4 shows causes of exclusion and mortality of these patients.

#### *Per protocol analysis*

One hundred and fifty-seven patients in the amoxicillin-clavulanate group and 166 in the ceftriaxone group were evaluable per protocol. Nine and 11 patients, respectively, were not assessable at the long-term follow-up visit (3 and 5 patients in good health refused to attend the visit, 3 and 4 patients died for cause unrelated to infection, 2 and 2 patients could not be located, and AIDS was diagnosed in one patient in the amoxicillin-clavulanate group). As shown in Table 3, there were no differences in clinical efficacy and mortality between groups. Overall, 38 patients had an unsatisfactory response throughout the study. Criteria for considering these patients as failures are summarized in Table 5. Bacteriological efficacy, assessed in 137 cases, was 92.4 and 95.8%, respectively.

#### *Antibiotic susceptibilities and pneumococcal serogroups/types*

Overall, 88.9% of the isolated pathogens were susceptible to amoxicillin-clavulanate, and 89.6% were susceptible to ceftriaxone. Susceptibilities of 105 *S. pneumoniae* strains are shown in Table 6. There were four (3.8%) strains of pneumococci with penicillin MICs of 4 µg/mL, and 11 (10.5%) strains showed multiple-resistance. MICs of amoxicillin (and amoxicillin-clavulanate) and ceftriaxone were similar, ranging from 0.015 to 2 µg/mL. Five strains showed a MIC of 2 µg/mL for amoxicillin (2 in the amoxicillin-clavulanate group and 3 in the ceftriaxone group) and four strains had a MIC of 2 µg/mL for ceftriaxone (2 and 2). Twenty-two different serogroups/types (SGT) were found among the 105 pneumococci isolates. Eight SGT accounted 79.8% of strains (83/105). The more frequent SGT were: 3 (34.3%); 8 (11.4%); 4 (7.6%); 19 (6.7%); 14 (5.7%); 9 (5.7%); 23 (4.8%), and 6 (2.9%).

Among the 28 *H. influenzae* isolates, β-lactamase production was detected in 17.9% of strains and no strain was resistant to the study drugs.

#### *Pneumococcal pneumonia*

There were 116 evaluate patients with proved pneumococcal pneumonia; 53 received amoxicillin-clavulanate and 63 ceftriaxone. Rates of high-level penicillin resistance were similar (8.2 and 10.2%). Table 7 shows treatment and outcomes of these patients. There were seven early clinical failures (four amoxicillin-clavulanate and three ceftriaxone), none of them presumably related to antibiotic resistance. Clinical efficacy at the end of therapy was 90.6 and 88.9%, respectively (95% C.I. of the difference, -9.3% to +12.7%). Mortality at 30 days was 9.4 and 11.1%, respectively. A satisfactory outcome at the end of therapy was observed in 76 (90.5%) of patients with penicillin-susceptible strains and in 18 (85.7%) of patients with penicillin-resistant strains ( $p = 0.81$ ). No relapses were observed at long-term follow-up. A detailed analysis of patients with pneumococcal pneumonia who were classified as failures at any assessment is provided in Table 8.

Among patients receiving amoxicillin-clavulanate, a satis-

TABLE 3. CLINICAL EFFICACY AND OUTCOME BY INTENTION-TO-TREAT AND PER PROTOCOL ANALYSES

| Assessments               | Intention-to-treat                     |                            |  | Per protocol                           |                            |  |
|---------------------------|--|----------------------------|--|--|----------------------------|--|
|                           | Amoxicillin-clavulanate<br>(No. = 184) | Ceftriaxone<br>(No. = 194) | p<br>(95% CI of the difference) <sup>a</sup> | Amoxicillin-clavulanate<br>(No. = 157) | Ceftriaxone<br>(No. = 166) | p<br>(95% CI of the difference) <sup>a</sup> |
| Early assessment          |  |                            |  |  |                            |  |
| Improvement               | 157 (85.3)                             | 169 (87.1)                 | 0.67   | 145 (92.4)                             | 158 (95.2)                 | 0.29   |
| Failure                   | 20 (10.9)                              | 19 (9.8)                   | (-8.8% to +5.2%)                             | 12 (7.6)                               | 8 (4.8)                    | (-8.1% to +2.5%)                             |
| End of therapy assessment |  |                            |  |  |                            |  |
| Cured                     | 146 (79.3)                             | 157 (80.9)                 | 0.68   | 137 (87.3)                             | 149 (89.8)                 | 0.48   |
| Failure                   | 31 (16.8)                              | 31 (16.0)                  | (-9.6% to +6.4%)                             | 20 (13.5)                              | 17 (10.2)                  | (-9.5% to +4.5%)                             |
| Final assessment          |  |                            |  |  |                            |  |
| No. patients              | 184                                    | 194                        | 0.78   | 148                                    | 155                        |  |
| Cured                     | 136 (73.9)                             | 144 (74.2)                 | (-8.7% to +8.1%)                             | 128 (86.5)                             | 137 (88.4)                 | 0.61   |
| Failure                   | 31 (16.8)                              | 33 (17.0)                  |  | 20 (13.5)                              | 18 (11.6)                  | (-9.4% to +5.6%)                             |
| Unevaluable               | 17 (9.2)                               | 17 (8.8)                   |  |  |                            |  |
| Overall mortality         | 19 (10.3)                              | 17 (8.8)                   |  | 15 (9.5)                               | 16 (9.6)                   |  |

<sup>a</sup>95% Confidence interval of the difference (amoxicillin-clavulanate minus ceftriaxone).

TABLE 4. PATIENTS EXCLUDED AFTER RANDOMIZATION: CAUSES AND OUTCOME

| <i>Causes of exclusion</i> | <i>Amoxicillin-clavulanate</i> | <i>Ceftriaxone</i> |
|----------------------------|--------------------------------|--------------------|
| No. of patients            | 27                             | 28                 |
| Misrandomization           | 10                             | 8                  |
| No pneumonia               | 7                              | 5                  |
| No severity criteria       | 3                              | —                  |
| AIDS                       | —                              | 2                  |
| Unresponsive shock         | —                              | 1                  |
| Protocol violation         | 3                              | 7                  |
| Atypical agents            | 11                             | 11                 |
| <i>Legionella</i>          | 4                              | 3                  |
| Atypical                   | 6                              | 5                  |
| Others                     | 1                              | 3                  |
| Aspiration pneumonia       | 3                              | 2                  |
| Overall mortality          | 4                              | 1                  |

factory outcome at the end of therapy was observed in 39 (88.6%) of amoxicillin-susceptible strains and in 5 (100%) of amoxicillin-resistant strains ( $p = 0.98$ ). Among patients receiving ceftriaxone, a satisfactory outcome at the end of therapy was observed in 44 (91.7%) of cephalosporin-susceptible strains and in 6 (75.0%) of cephalosporin-resistant strains ( $p = 0.42$ ).

**DISCUSSION**

The worldwide emergence of penicillin resistance among *Streptococcus pneumoniae* has complicated the treatment of pneumococcal pneumonia and, consequently, the empirical therapy of the entire group of patients with suspected bacterial CAP. To date, the clinical relevance of “*in vitro*” resistance to betalactams in these infections is unclear and there is no universally accepted “gold standard” for the treatment of resistant

pneumococcal pneumonia (16,18,32). In this randomized trial evaluating a large population of patients with CAP who fulfilled previously defined hospitalization criteria, amoxicillin-clavulanate and ceftriaxone were found to be equally safe and effective. Rates of failure and mortality were in the low range of those reported for moderate-to-severe CAP, both in the total group of patients and in the subset of patients with proven pneumococcal pneumonia.<sup>11,12,38</sup> We also found no significant difference in outcomes attributable to penicillin susceptibility of pneumococcal strains and no differences attributable to treatment regimens in penicillin and cephalosporin-resistant pneumococcal pneumonia. Nevertheless, when interpreting our findings it should be kept in mind the small number of highly resistant strains isolated in our trial.

Our data are useful for assessing the efficacy of betalactam therapy for CAP of suspected bacterial etiology, in an area of high prevalence of penicillin-resistant pneumococci, especially taking into account that only a low proportion of patients re-

TABLE 5. CAUSES OF FAILURE IN EVALUABLE PATIENTS ACCORDING TO TREATMENT GROUP

| <i>Cause of failure</i>   | <i>Amoxicillin-clavulanate</i> | <i>Ceftriaxone</i> |
|---------------------------|--------------------------------|--------------------|
| No. of patients           | 20                             | 18                 |
| Early assessment          | 12                             | 8                  |
| Died before assessment    | 7                              | 4                  |
| No improvement            | 2                              | —                  |
| Clinical worsening        | 3                              | 4                  |
| Acute respiratory failure | 3                              | 4                  |
| Hemodynamic failure       | —                              | 2                  |
| Radiological progression  | 2                              | 3                  |
| End of therapy assessment | 8                              | 9                  |
| Superinfection            | 2                              | 2                  |
| Adverse effects           | 1                              | —                  |
| Change of therapy         | 1                              | 1                  |
| Death                     | 4                              | 6                  |
| Pneumonia related         | 3                              | 2                  |
| Nonrelated to pneumonia   | 1                              | 4                  |
| Final assessment          | —                              | 1                  |
| Superinfection            | —                              | 1                  |

TABLE 6. *IN VITRO* ACTIVITY OF 8 ANTIMICROBIAL AGENTS AGAINST 105 *STREPTOCOCCUS PNEUMONIAE* STRAINS

| <i>Antimicrobial agent</i>                 | <i>Minimal inhibitory concentration (µg/mL)</i> |      |      |      |      |     |   |    |    |   |    | <i>MIC<sub>50</sub></i> | <i>MIC<sub>90</sub></i><br>(µg/mL) | %R <sup>a</sup> | %I <sup>a</sup> |      |      |      |
|--|---|------|------|------|------|-----|---|----|----|---|----|-------------------------|------------------------------------|-----------------|-----------------|------|------|------|
|  | ≤0.01   | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2  | 4  | 8 | 16 |                         |                                    |                 |                 | 32   | ≥64  |      |
|  | no. of isolates inhibited                       |      |      |      |      |     |   |    |    |   |    |                         |                                    |                 |                 |      |      |      |
| Penicillin                                 | 69  | 14   | 1    | 2    | 3    | 6   | 6 | 6  | 4  |   |    |                         |                                    |                 | ≤0.01           | 1    | 9.5  | 10.5 |
| Amoxicillin/clavulanate <sup>b</sup>       | 60  | 23   |      | 1    | 3    | 5   | 8 | 5  |    |   |    |                         |                                    |                 | ≤0.01           | 1    | 4.8  | 7.6  |
| Ceftriaxone                                | 73  | 9    | 2    | 3    | 1    | 5   | 8 | 4  |    |   |    |                         |                                    |                 | ≤0.01           | 1    | 3.8  | 7.6  |
| Erythromycin                               |   | 3    | 67   | 30   |      |     |   |    |    |   |    |                         |                                    |                 | 0.06            | 0.12 | 4.8  | 0    |
| Clindamycin                                |   |      | 70   | 30   |      |     |   |    |    |   |    |                         |                                    |                 | 0.06            | 0.12 | 4.8  | 0    |
| Tetracycline                               |   |      |      | 6    | 48   | 29  | 4 | 1  | 1  | 7 | 3  |                         |                                    |                 | 0.25            | 16   | 18.1 | 0    |
| Chloramphenicol                            |   |      |      | 1    | 9    | 76  | 6 | 10 | 3  |   |    |                         |                                    |                 | 2               | 8    | 12.4 | 0    |
| Trimethoprim/sulfamethoxazole <sup>c</sup> |   |      |      | 31   | 39   | 10  | 1 | 5  | 13 | 6 |    |                         |                                    |                 | 0.5             | 4    | 22.8 | 0.9  |

<sup>a</sup>R = resistant; I = intermediate; NCCLS, 1995 criteria.

<sup>b</sup>Amoxicillin clavulanate, ratio 2:1.

<sup>c</sup>Trimethoprim/sulfamethoxazole, ratio 1:19.

Diagnosis of pneumococcal pneumonia in 11 patients was performed by PCR and/or latex agglutination test; therefore no strains were available for susceptibility testing.



TABLE 7. TREATMENT AND OUTCOMES OF 116 PATIENTS WITH PNEUMOCOCCAL PNEUMONIA

| Outcomes  | Amoxicillin-clavulanate<br>n (%) | Ceftriaxone<br>n (%) |
|---|----------------------------------|----------------------|
| Patient nos.  | 53                               | 63                   |
| Length of therapy (mean $\pm$ SD)                       |                                  |                      |
| intravenous   | 5.5 $\pm$ 1.6                    | 6.2 $\pm$ 3.7        |
| complete  | 11.8 $\pm$ 9.9                   | 11.8 $\pm$ 5.7       |
| Combination macrolide therapy                           | 2 (3.8)                          | 5 (7.9)              |
| Mechanical ventilation                                  | 2 (3.8)                          | 3 (4.8)              |
| Time to defervescence (T $\leq$ 37.0°C) (mean $\pm$ SD) | 2.6 $\pm$ 2.2                    | 2.8 $\pm$ 3.6        |
| Length of hospital stay (mean $\pm$ SD)                 | 9.5 $\pm$ 5.0                    | 12.7 $\pm$ 13.0      |
| Adverse events  | 12 (22.6)                        | 11 (17.5)            |
| Overall mortality                                       | 5 (9.4)                          | 7 (11.1)             |
| early death <48 h                                       | 3 (5.7)                          | 2 (3.2)              |
| Clinical efficacy <sup>a</sup> (success/total)          | 48/53                            | 56/63                |
| bacteremic  | 12/14                            | 16/20                |
| MIC of penicillin                                       |                                  |                      |
| $\leq$ 0.06 $\mu$ g/mL                                  | 37/42                            | 39/42                |
| $\geq$ 0.12–1 $\mu$ g/mL                                | 3/3                              | 7/8                  |
| 2 $\mu$ g/mL  | 4/4                              | 4/6                  |
| Bacteriological efficacy <sup>b</sup> (success/total)   | 45/46                            | 52/53                |

Baseline clinical characteristics were similar in the two groups. No differences were statistically significant.

<sup>a</sup>At the end of therapy.

<sup>b</sup>Two failures due to superinfection.

ceived combination macrolide therapy. Our data show that both amoxicillin-clavulanate and ceftriaxone can be used against pneumococci with penicillin MICs of 4  $\mu$ g/mL. This finding may be relevant for future recommendations, because a substantial number of pneumococci isolated from patients with CAP have penicillin MICs between 1 and 4  $\mu$ g/mL, and it is very unusual to isolate strains with higher MICs.<sup>8,21,24,34</sup> In our country, penicillin resistance increased dramatically during the 1980s, but it has remained stable since then. A recent nationwide survey reported a resistance rate of approximately 40% while cephalosporin resistance is increasing slightly.<sup>9,22,30</sup> In some European countries and the United States, with lower figures, there has been a marked increase in the prevalence of drug resistance in the 1990s, similar to the rise recorded in Spain in the previous decade.<sup>6,37</sup> On the other hand, the level of resistance also appears to remain stable or to increase very slowly, and currently it is very rare to isolate pneumococcal strains with ceftriaxone MICs higher than 2  $\mu$ g/mL. The frequency of these strains has been reported to be less than 0.5% in Spain,<sup>8</sup> and we did not identify any in this trial. Nevertheless, the importance of monitoring continuously the sensitivities of pneumococcal isolates should be stressed because the proportion of highly resistant strains may increase in the future.

In our study, the response to betalactam therapy did not differ between patients with pneumococcal pneumonia due to resistant strains and patients with susceptible strains. Although the more frequent isolation of highly resistant strains might have strengthened our conclusions, our findings, involving adult patients, are in concordance with two recent retrospective studies involving pediatric patients. These studies compared the outcomes of patients with pneumococcal pneumonia due to either penicillin susceptible or resistant strains and found that children responded equally well to betalactams regardless of the penicillin susceptibility of their pneumococcal isolates.<sup>5,36</sup> In this

regard, it should be noted that the NCCLS has recently modified the criteria to define amoxicillin resistance, increasing the MIC breakpoint from 1 to 4  $\mu$ g/mL to define intermediate susceptibility, and from  $\geq$ 2 to  $\geq$ 8  $\mu$ g/mL to define resistance.<sup>29</sup> Nevertheless, the criteria for the extended spectrum cephalosporins have not yet been changed.<sup>28,29</sup> Our view is that current MIC breakpoints for cephalosporin resistance should also be redefined for the treatment of nonmeningeal pneumococcal invasive disease.

The low number of highly penicillin resistant strains (MIC  $\geq$  2  $\mu$ g/mL) found in the study is a reasonable reflection of the real situation of the resistance among pneumococci causing CAP in our area. In fact, rates of penicillin and multiple drug resistance in this patient population were lower than those reported by us in previous studies, which also included pneumococcal isolates from different patient populations and sources.<sup>21,30,31</sup> This difference may be explained by the fact that the present study did not include immunosuppressed patients (AIDS and cancer patients), nosocomial pneumonias, nor sputum isolates from chronic bronchitics. In addition, the distribution of SGTs found in our study differed from those found in previous studies.<sup>15,21</sup> In fact, more than one third of the pneumococci belonged to SGT 3, followed by SGTs 8 and 4, which are usually penicillin susceptible. SGTs 19 and 23, which are associated with multiresistant patterns, were observed in frequencies similar to those in previous studies, while SGT 14, 9, and 6 were less frequently found.<sup>8,21</sup>

The concern with the poor response to betalactams may lead to frequent use of other antimicrobial agents active against resistant pneumococci, such as glycopeptides or the new fluoroquinolones. Nowadays, there is general agreement that vancomycin should be reserved as much as possible to avoid the emergence of resistance among other Gram-positive organisms. Regarding the newest fluoroquinolones, although recent clini-

TABLE 8. CLINICAL CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH PNEUMOCOCCAL PNEUMONIA WHO WERE CLASSIFIED AS FAILURES AT ANY ASSESSMENT

| Patient no.             | Age/Sex | Underlying disease | Source of diagnosis                  | MIC of penicillin | MIC of amoxicillin | MIC of ceftriaxone | Assessment     | Cause of failure   | Outcome | Day of death | Cause of death                         |
|-------------------------|---------|--------------------|--------------------------------------|-------------------|--------------------|--------------------|----------------|--------------------|---------|--------------|--|
| Amoxicillin-clavulanate |         |                    |                                      |                   |                    |                    |                |                    |         |              |  |
| 1                       | 70/M    | COPD <sup>a</sup>  | Sputum                               | 0.030             | 0.030              | 0.015              | Early          | Clinical worsening | Died    | 24           | <i>E. cloacae</i> nosocomial pneumonia |
| 2                       | 35/M    | Splenectomy        | Blood                                | 0.015             | 0.015              | 0.015              | Early          | Death              | Died    | 1            | Sepsis                                 |
| 3                       | 80/M    | Diabetes           | Sputum                               | 0.015             | 0.015              | 0.015              | Early          | Death              | Died    | 1            | Respiratory failure                    |
| 4                       | 73/M    | Liver cirrhosis    | Blood                                | 0.015             | 0.030              | 0.015              | Early          | Death              | Died    | 1            | Respiratory failure                    |
| 5                       | 68/M    | COPD               | Sputum                               | 0.030             | 0.015              | 0.030              | End of therapy | Death              | Died    | 8            | Respiratory failure                    |
| Ceftriaxone             |         |                    |                                      |                   |                    |                    |                |                    |         |              |  |
| 6                       | 30/F    | —                  | LA <sup>a</sup> (+) pleural effusion | NA                | NA                 | NA                 | Early          | Clinical worsening | Cured   |              |  |
| 7                       | 92/F    | CHF <sup>a</sup>   | Blood                                | 2                 | 1                  | 1                  | Early          | Death              | Died    | 1            | Sepsis                                 |
| 8                       | 67/M    | COPD               | TNA <sup>a</sup>                     | 0.015             | 0.015              | 0.015              | Early          | Death              | Died    | 2            | Respiratory failure                    |
| 9                       | 60/M    | Liver cirrhosis    | Empyema                              | 1                 | 1/0.5              | 0.5                | End of therapy | Superinfection     | Died    | 23           | MRSA <sup>a</sup> sepsis               |
| 10                      | 80/M    | CRF <sup>a</sup>   | Blood                                | 4                 | 2                  | 2                  | End of therapy | Death              | Died    | 12           | Gut ischemia                           |
| 11                      | 42/F    | Liver cirrhosis    | Blood                                | 0.015             | 0.015              | 0.015              | End of therapy | Death              | Died    | 9            | Multifactorial failure                 |
| 12                      | 77/M    | —                  | TNA, blood, empyema                  | 0.015             | 0.015              | 0.015              | End of therapy | Death              | Died    | 15           | Pulmonary thromboembolism              |

<sup>a</sup>COPD, chronic obstructive pulmonary disease; CHF, chronic heart failure; CRF, chronic renal failure; LA, latex agglutination test; TNA, trans thoracic needle aspiration; and MRSA, methicillin-resistant *S. aureus*.

cal data support their use for the treatment of respiratory infections,<sup>10</sup> including those due to penicillin-resistant pneumococci, controlled studies focusing on patients with severe pneumococcal pneumonia and bacteremia are still insufficient.<sup>17</sup> In a large multicenter randomized study comparing levofloxacin with ceftriaxone/cefuroxime, File *et al.*<sup>10</sup> found that levofloxacin eradicated 100% of pneumococcal isolates, although the number of bacteremic cases was very low and no penicillin-resistant strain was isolated in this study. Moreover, recent data demonstrate that the prevalence of pneumococci with reduced susceptibility to fluoroquinolones is increasing in some countries, probably as a consequence of selective pressure from the increased use of fluoroquinolones.<sup>4</sup> These data suggest prudent use of these agents, reserving them for indications where they offer a clear therapeutic advantage.<sup>4,16,20</sup> Thus, based on the current levels of resistance, physicians may feel comfortable with the continuous use of appropriate betalactams in patients with proven or suspected pneumococcal pneumonia, adding a macrolide or a fluoroquinolone when *Legionella* or an atypical pathogen cannot be reasonably ruled out. When choosing the most appropriate betalactam agent, it should be borne in mind that activity against penicillin-resistant pneumococci varies greatly among different betalactams and that cephalosporins with poor activity or an unfavorable pharmacodynamic profile should be avoided.<sup>21,33</sup> In this regard it should be noted that at the dosage used of parenteral amoxicillin and ceftriaxone, the plasma levels of both antibiotics are above 8 µg/mL during a large percentage of the dosing interval.<sup>26,35</sup>

In conclusion, in our area where penicillin resistance is prevalent, sequential intravenous/oral amoxicillin-clavulanate and parenteral ceftriaxone were effective and safe for empirical treatment of hospitalized patients with acute bacterial pneumonia, including cases due to pneumococcal strains with penicillin MICs up to 4 µg/mL. The use of appropriate betalactams in patients with pneumococcal pneumonia is reliable at the current level of resistance.

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