

# Treatment and Course of Community-Acquired Pneumonia Caused by Atypical Pathogens

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**OBJECTIVE:** To study the course of disease and outcomes in a group of patients with community-acquired pneumonia caused by atypical pathogens (*Mycoplasma pneumoniae*, *Legionella* species, *Coxiella burnetii*, and *Chlamydomphila pneumoniae*) according to the empiric treatment received.

**PATIENTS AND METHODS:** Of a total of 390 patients admitted to our hospital with pneumonia between January 1996 and February 2001, the causative microorganism was an atypical pathogen in 89 cases. Patients were divided retrospectively into 2 groups according to the empiric treatment they received: group A, who had received an antibiotic regimen (quinolones or macrolides) that provided coverage for atypical pathogens; and group B, who had received treatment that did not provide such coverage. Clinical course was assessed in terms of the differences between the 2 groups in length of hospital stay, radiographic resolution, readmission at 30 days after discharge, and mortality.

**RESULTS:** A total of 89 patients with pneumonia caused by atypical pathogens (39 in group A and 50 in group B) were studied. No significant between-group differences in the variables were found.

**CONCLUSIONS:** In this group of patients hospitalized for community-acquired pneumonia, antibiotic regimens providing coverage for atypical pathogens did not improve either clinical or radiographic evolution.

**Key words:** Antibiotic treatment for pneumonia. Community-acquired pneumonia. Atypical pneumonia.

Neumonía adquirida en la comunidad por gérmenes atípicos: tratamiento y evolución

**OBJETIVO:** Estudiar la evolución de un grupo de neumonías extrahospitalarias causadas por gérmenes atípicos (*Mycoplasma pneumoniae*, *Legionella* spp., *Coxiella burnetii* y *Chlamydomphila pneumoniae*) en función del tratamiento empírico recibido.

**PACIENTES Y MÉTODOS:** Entre enero de 1996 y febrero de 2001 ingresaron en nuestra unidad 390 casos de neumonía, de los que 89 estaban causados por gérmenes atípicos. Los pacientes se dividieron retrospectivamente en 2 grupos según el tratamiento empírico pautado: grupo A, al que se había proporcionado cobertura frente a gérmenes atípicos (quinolonas o macrólidos), y grupo B, al que no se había proporcionado dicha cobertura. Se estudió la evolución según las diferencias entre ambos grupos en la estancia hospitalaria, la resolución radiológica, el reingreso en el primer mes tras el alta y la mortalidad.

**RESULTADOS:** El grupo de estudio lo constituyeron 89 pacientes con neumonía causada por gérmenes atípicos (39 en el grupo A y 50 en el B). Las variables estudiadas no mostraron diferencias significativas entre ambos grupos.

**CONCLUSIONES:** En nuestra serie de neumonías extrahospitalarias la cobertura antibiótica frente a gérmenes atípicos no mejoró la evolución clínica y radiológica de los pacientes.

**Palabras clave:** Tratamiento antibiótico de la neumonía. Neumonía adquirida en la comunidad. Neumonía atípica.

## Introduction

Community-acquired pneumonia (CAP) is a highly prevalent disease that requires initial empiric treatment. The selection of an appropriate antibiotic regimen for these patients is considered to have a substantial influence on prognosis, and this topic has been dealt with at length in the consensus statements on CAP of various scientific societies.<sup>1-4</sup> Among the microorganisms that cause CAP, the so-called "atypical" pathogens (*Mycoplasma pneumoniae*, *Coxiella burnetii*, *Chlamydomphila pneumoniae*, and *Legionella* species) have given rise to considerable controversy, regarding both their real incidence and the

clinical importance of their presence.<sup>5-8</sup> It has, nevertheless, been proposed that the empiric treatment of patients with CAP who require hospitalization should routinely provide coverage for these pathogens.<sup>1</sup>

Our objective was to study the clinical course of CAP caused by atypical pathogens according to empiric treatment prescribed in order to ascertain whether the use of antibiotics active against this group of pathogens influenced outcome.

## Patients and Methods

This prospective study consecutively enrolled 390 patients who were admitted to our hospital with CAP between January 1996 and February 2001. CAP was defined as the presence of a new pulmonary infiltrate on a chest radiograph found in association with signs and symptoms indicative of pneumonia, such as cough, purulent sputum, fever, pleuritic chest pain, and/or

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leukocytosis. Immunodeficient patients and patients whose pneumonia might be nosocomial were excluded from the study.

CAP was attributed to an atypical pathogen if there was a 4-fold increase in serum antibodies between paired samples obtained during the acute phase and subsequently during the convalescent phase (separated by a 4-week interval), when *Legionella* antigen was detected in urine using chromatography, or when immunoglobulin M against *C pneumoniae* was found in blood during the acute phase. The serological techniques used were passive agglutination for *M pneumoniae* and indirect immunofluorescence for *Coxiella*, *Chlamydomphila*, and *Legionella* species.

*Procedures*

A complete medical history was taken in the emergency department for all patients diagnosed with CAP. This was complemented by a physical examination, a basic battery of tests (complete blood count, blood sugar, liver function, arterial blood gas analysis), and a chest radiograph. Based on the findings and in accordance with the criteria established in the guidelines, a decision was taken as to whether the patient should be admitted and what antibiotic regimen should be prescribed.<sup>2</sup> The study protocol required the following information to be collected for each patient: demographic profile (age and sex) and associated morbidity factors based on the relevant clinical, analytical, functional, and pathological criteria (chronic obstructive pulmonary disease, diabetes mellitus, heart disease, liver disease, active cancer, alcoholism, chronic renal insufficiency, and/or degenerative neurological disease). Radiographic involvement was classified as unilobar or multilobar, and the presence of pleural effusion was recorded.

Clinical course was studied in terms of the following variables: length of hospital stay, timing of radiographic resolution, readmission within 30 days of discharge, and mortality. Radiographic resolution was defined as the disappearance of the consolidation that gave rise to the diagnosis of pneumonia, and the assessment was made jointly by any 2 of the authors.

The following diagnostic tests were performed during hospitalization: blood cultures, Gram stain and culture of sputum (if phlegm was expectorated), initial serological tests for *C pneumoniae*, *M pneumoniae*, *Legionella* species, and *C burnetii*, pleural fluid culture (in patients with effusion), and urinary *Legionella* antigen test (during the last 2 years of the study only).

The patients returned for a clinical and radiographic check-up 4 weeks after discharge, and samples for the second set of serological tests were also obtained at this time. Patients were monitored monthly thereafter until the pneumonia had completely resolved.

Severity was assessed retrospectively using the prediction rule developed by Fine et al,<sup>8</sup> and the patients were grouped into 2 categories: a) low risk, including classes I, II, and III; and b) high risk, including classes IV and V.<sup>9</sup>

*Study Groups*

The patients who required hospitalization and were diagnosed as having pneumonia caused by an atypical pathogen were assigned to 1 of 2 groups depending on the empirical antibiotic treatment they had received: group A was made up of patients who had been treated with a regimen providing coverage for atypical pathogens (third- or fourth-generation quinolones or a macrolide), and group B included patients whose regimen did not include such antibiotics.

*Statistical Analysis*

Quantitative variables were analyzed by way of a comparison of means (the Student *t* test) and qualitative

variables with the  $\chi^2$  test. Statistical significance was set at *P* less than .05.

**Results**

*General Characteristics*

A paired serological test was performed in 276 (71%) of the 390 patients, and 89 cases of atypical pneumonia were diagnosed (22.8% of the total). These 89 patients formed the study group; 60 (67.4%) were men. The mean (SD) age was 52.7 (20.9) years, and 46 patients (53%) had some kind of comorbidity. The main comorbidities were chronic obstructive pulmonary disease in 12 cases, diabetes mellitus in 15, alcoholism in 7, heart disease in 11, active cancer in 9, and degenerative neurological disease in 9. Applying the Fine prediction rule, 57 cases (64%) fell into classes I, II, or III, and 32 (36%) into classes IV and V.

In addition to the serological tests, blood cultures were obtained for 45 cases (leading to 1 diagnosis of *Neisseria meningitidis* infection). A sputum culture was ordered for 40 patients although this test was deemed to have been appropriate in only 19 of these cases. These cultures led to 5 etiologic diagnoses (2 of *Pseudomona aeruginosa* infection, 2 of *Klebsiella pneumoniae*, and 1 of *Streptococcus pneumoniae*). Pleural fluid culture, obtained for 14 cases, yielded 1 diagnosis (*S pneumoniae*).

Table 1 shows the microbiological diagnoses. More than 1 pathogen was isolated in 8 cases (8.9%). The etiology of these mixed infections was as follows: *S pneumoniae-M pneumoniae* (1 case), *P aeruginosa-C burnetii* (2 cases), *K pneumoniae-C burnetii* (2 cases), *S pneumoniae-C burnetii* (1 case), *N meningitidis-C pneumoniae* (1 case), and *Legionella species-C burnetii* (1 case).

The following treatment regimens were used: 46 patients (52%) received only  $\beta$ -lactam antibiotics; 5 (5.4%) were treated with a macrolide; 17 patients (19%) received a combination of macrolides and  $\beta$ -lactam antibiotics; 15 (17%) received third-generation quinolones (levofloxacin); and 6 (6.6%) were treated with other combinations (2 of which included levofloxacin). The  $\beta$ -lactam antibiotics used were third-generation cephalosporins and amoxicillin-clavulanic acid. The macrolide was clarithromycin in all cases.

*Group Composition*

Group A comprised 39 patients with a mean age of 41.05 years, and Group B, 50 patients with a mean age of 60.4 years. Table 2 shows the data on comorbidity, radiographic presentation, and severity. There were

TABLE 1  
Diagnostic Methods and Microbiological Diagnoses

Pathogen	Serology	Urinary Antigen	Total
<i>Mycoplasma pneumoniae</i>	21		21 (24%)
<i>Coxiella burnetii</i>	35		35 (39%)
<i>Legionella</i> species	6	2	8 (9%)
<i>Chamydophila pneumoniae</i>	25		25 (28%)

TABLE 2  
Factors Associated With Pneumonia\*

	With Coverage for Atypical Pathogens (n=39)	Without Coverage for Atypical Pathogens (n=50)	P
Mean (SD) age, y	41.01	61.4	.003
Comorbidity	14 (35%)	32 (64%)	.01
Alcoholism	0	7	.01
Heart disease	2	9	NS
Diabetes mellitus	4	11	NS
COPD	2	10	.03
Degenerative neurological disease	2	7	NS
Cancer	1	8	.03
Others	3		
Pleural effusion	2	14	.04
Complicated pleural effusion	1	5	.04
Laboratory findings			
Kidney failure	2	3	NS
Respiratory insufficiency	11	12	NS
Radiographic presentation			
Unilobar consolidation	18 (46%)	45 (90%)	.001
Multilobar consolidation	21 (54%)	5 (10%)	.0001
Fine class			
I, II, or III	30 (77%)	27 (54%)	.02
IV or V	9 (23%)	23 (46%)	.02

\*COPD indicates chronic obstructive pulmonary disease; NS, not significant.

significant differences between the 2 groups in age, comorbidity, severity, and presence of pleural effusion.

#### Influence of the Choice of Antibiotic Therapy

The influence of the antibiotic regimen used was assessed in terms of the following outcome variables: length of hospital stay, mortality, readmission at 30 days, and radiographic resolution. As can be seen in Table 3, treatment with an antibiotic regimen providing specific coverage against atypical pathogens had no significant impact on these variables.

While 4 patients in Group B were readmitted within a month of discharge, the readmission was related to the pneumonia episode in only 1 case (empyema). In the other 3 cases, readmission was due to a comorbid condition (cancer-related surgery, congestive heart failure, and urine retention).

#### Discussion

In our study, antibiotic coverage against atypical pathogens did not improve clinical or radiographic course in patients with CAP.

Recent guidelines<sup>1</sup> recommend routine coverage of atypical pathogens in order to reduce length of hospital stay and improve survival in CAP based on the results of 2 nonrandomized studies.<sup>10,11</sup> Some authors have criticized this recommendation for various reasons, including the effect of methodological limitations on the conclusions that can be drawn from these studies.<sup>5</sup> Moreover, it should be noted that neither of the studies included many cases involving atypical pathogens. Our main contribution is, therefore, to provide data on a

TABLE 3  
Outcome Measures\*

	With Cover for Atypical Pathogens	Without Cover for Atypical Pathogens	P
Mean (SD) length of stay, d	11.40 (8.4)	10.66 (5.7)	NS
Death	1	1	NS
Readmission 1 month after discharge	0	1	NS
Radiographic resolution 1 month after discharge	22	24	NS
Radiographic resolution 2 months after discharge	31	31	NS

\*NS indicates not significant.

large group of patients with pneumonia caused by such microorganisms. Since the fundamental argument for routinely broadening the therapeutic spectrum in patients with CAP is to provide coverage against atypical pathogens, it is of the utmost importance to clarify the actual role played by these microorganisms in the etiology, pathogenesis, clinical manifestations, and course of the infection (all of which are still the object of research and controversy).<sup>7</sup>

Unlike Stahl et al<sup>10</sup> and Gleason et al,<sup>11</sup> whose studies included few microbiological diagnoses, we specifically studied patients with CAP caused by an atypical pathogen and found no significant differences in either mean length of hospital stay or other outcome variables between the groups that were and were not specifically treated against such microorganisms. With respect to mortality, the fact that our protocol called for paired serological tests to establish a diagnosis probably meant that the severity of the cases included in our study was lower since the design excluded patients who died in the first few days. This could explain the differences between our findings and those of Gleason et al,<sup>11</sup> who reported differences in mortality at 30 days. Paradoxically, however, when the data was analyzed by severity using Fine's prediction rule we found that although patients with severe disease had not usually received coverage for atypical pathogens neither mortality nor mean length of stay was higher in this group. Furthermore, we want to make the point that in the assessment of the efficacy of an antibiotic regimen, particularly in patients with mild to moderate pneumonia, it is possible that mean length of hospital stay and mortality are not the variables that provide the most information since mortality will be low and length of hospital stay is influenced by many factors.<sup>12,13</sup> Consequently, we used readmission within 1 month of discharge and radiographic resolution as additional variables in our comparison of the 2 therapeutic groups and found no significant between-group differences in these variables.

It should be noted that 7 of the 8 patients with pneumonia caused by *Legionella* species were treated with macrolides or quinolones, and the outcome in the eighth patient was good despite the fact that he was treated with a  $\beta$ -lactam antibiotic.

Our study suffers from the limitations affecting any nonrandomized study, including the fact that the groups

were not homogeneous in terms of age, radiographic presentation, and severity (Table 3). However, even when the data were analyzed by severity, no significant differences were found in the outcome measures.

Moreover, given that appropriate therapy is generally a key factor in the prognosis of any infection,<sup>14</sup> it is interesting that it does not appear to be important either in the present case series or in another similar study<sup>15</sup> in which treatment providing coverage against atypical pathogens did not influence mortality. These findings raise doubts about the real impact of such treatment on the disease process. It is possible that the rate of spontaneous cure in this subgroup of pneumonia cases may be very high or that the atypical pathogens may only be coinfectants that facilitate the arrival of other microorganisms to the lung.<sup>6,7</sup> Other authors have suggested that serological diagnoses may not be entirely reliable and that there could be an unknown percentage of overdiagnosis.<sup>16</sup> It is important to note in this respect, however, that what may be the case for *M pneumoniae*, *C burnetii*, and *C pneumoniae* does not apply to *Legionella* species since appropriate antimicrobial coverage has considerable influence on prognosis in patients infected with *Legionella* species.

Another factor that could explain the differences between our findings and those of Stahl et al<sup>10</sup> and Gleason et al<sup>11</sup> is the anti-inflammatory effect of the antibiotics and especially of the macrolides.<sup>17</sup> This effect is greater in more severe cases in which inflammation is more marked. As there was a high percentage of moderate cases of pneumonia in our series, this factor may have been less important. In a recently published study, Baddour et al<sup>18</sup> demonstrated the efficacy of combination antibiotic therapy in critically ill patients with pneumonia.

There are 2 points of particular interest with respect to microbiological diagnoses in our study: the high frequency of *C burnetii* (9% of the total), and the scant presence of *Legionella* species (2% of the total). In a review of 41 studies of patients with CAP carried out in various European countries,<sup>19</sup> only 0.8% of cases were documented as Q fever whereas *Legionella* species was the cause in up to 4.9% of patients hospitalized with pneumonia. The peculiarities of our case series may be due to the geographical variation attributed to these pathogens (and particularly to *C burnetii*),<sup>19</sup> and it is also possible that *Legionella* species may have been underdiagnosed because most cases were diagnosed by serology so that late seroconversion phenomena could have played a part.

In conclusion, in this series of CAP cases in which atypical pathogens were detected, antibiotic therapy providing coverage against atypical microorganisms did not improve outcome measures. In spite of its limitations, the present study supports the view recently expressed by other authors<sup>20,21</sup> that there is still a place for monotherapy with  $\beta$ -lactam antibiotics in patients with mild to moderate CAP. Furthermore, as noted in the latest guidelines for the diagnosis and treatment of CAP published by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR),<sup>22</sup> there is still only scant evidence on which to base precise recommendations concerning antimicrobial treatment,

and randomized trials to further clarify this aspect of CAP treatment are perhaps necessary.

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