Comparative Study of the Clinical Presentation of Legionella Pneumonia and Other Community-Acquired Pneumonias*

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The aim of this study was to compare the clinical, biological, and radiologic features of presentation in the emergency ward of community-acquired pneumonia (CAP) by *Legionella pneumophila* (LP) and other community-acquired bacterial pneumonias to help in early diagnosis of CAP by LP. Three hundred ninety-two patients with CAP were studied prospectively in the emergency department of a 600-bed university hospital. Univariate and multivariate analyses were performed to compare epidemiologic and demographic data and clinical, analytical, and radiologic features of presentation in 48 patients with CAP by LP and 125 patients with CAP by other bacterial etiology (68 by *Streptococcus pneumoniae*, 41 by *Chlamydia pneumoniae*, 5 by *Mycoplasma pneumoniae*, 4 by *Coxiella burnetii*, 3 by *Pseudomonas aeruginosa*, 2 by *Haemophilus influenzae*, and 2 by *Nocardia species*). Univariate analysis showed that CAP by LP was more frequent in middle-aged, male healthy (but alcohol drinking) patients than CAP by other etiology. Moreover, the lack of response to previous ß-lactamic drugs, headache, diarrhea, severe hyponatremia, and elevation in serum creatine kinase (CK) levels on presentation were more frequent in CAP by LP, while cough, expectoration, and thoracic pain were more frequent in CAP by other bacterial etiology. However, multivariate analysis only confirmed these differences with respect to lack of underlying disease, diarrhea, and elevation in the CK level. We conclude that detailed analysis of features of presentation of CAP allows suspicion of Legionnaire’s disease in the emergency department. The initiation of antibiotic treatment, including a macrolide, and the performance of rapid diagnostic techniques are mandatory in these cases.

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**Key words:** community-acquired infections; *Legionella pneumophila*; pneumonia, bacterial

**Abbreviations:** AST=aspartate aminotransferase; CAP=community-acquired pneumonia; CK=creatine kinase; LP= *Legionella pneumophila*

*Legionella pneumophila* (LP) is, in most studies, among the three most common causes of community-acquired pneumonia (CAP),¹⁻⁵ and it is the second-highest cause of severe pneumonia.⁶⁻⁸ Diagnosis is commonly performed retrospectively by serologic study or tardy by isolation in special culture mediums from clinical samples. The delay in the initiation of adequate treatment due to diagnostic tardiness negatively influences the prognosis of the disease.⁹⁻¹³

Since the first description of pneumonia by Legionella, some symptoms and laboratory features have been considered as characteristic of the disease.¹⁴ Nevertheless, the scarce comparative studies with other CAPs have reported contradictory results.³,¹⁵⁻¹⁹

Considering the incidence, severity, and diagnostic delay, well-founded clinical suspicion of CAP by LP in the emergency department may aid in the initiation of the most appropriate empiric treatment.

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and thus improve the prognosis of patients with the disease. Therefore, a comparative study of the features of clinical, radiologic, and analytical presentation of CAP by LP and CAP by other bacterial etiology was performed. The aim was to search for discriminative features that aid in the early diagnosis and treatment of CAP by LP.

**Materials and Methods**

**Patients**

From May 1994 to February 1996, we prospectively studied 392 patients with CAP who attended the emergency department of a 600-bed university hospital. We included patients >14 years of age with acute symptoms consistent with pneumonia and a new infiltrate on the chest radiograph at the time of hospital admission or within 24 h. Patients with some of the following criteria were excluded: discharge from the hospital <10 days before the onset of symptoms of pneumonia, suspicion of bronchoaspiration, obstructive pneumonia, or pulmonary tuberculosis. Residence in a nursing home, HIV infection, or pharmacologic immunosuppression were not criteria for exclusion. Forty-eight patients had CAP by LP and 125 patients were diagnosed as having CAP by other bacterial etiology. In 219 patients, the etiology was cataloged as low probability or not achieved, and they were excluded from this study. Clinical, analytical, and radiologic features of presentation, as well as other epidemiologic data, were collected in all the cases. Two serial blood cultures, sputum collection for Gram's analysis, and culture in the conventional media and BCYE-alfa medium were systematically performed. Two serum samples were obtained with 3 to 5 weeks of difference for detection of antibodies against LP serogroup 1 to 6 by immunofluorescence (Mero-IFA Slides; LaSybsem; S. Just Desvern, Spain), Coxiella burnetii by indirect immunofluorescence (Rickettsiam; Pasteur, France), Chlamydia psittaci and Chlamydia pneumoniae by microimmunofluorescence (Chlamydia MIF IgG; MRL Diagnostics; Cypress, Calif), and Mycoplasma pneumoniae by passive agglutination (Serodia-R-Mycoll; Fujirebio Inc; Tokyo, Japan). Urine was collected in the acute phase for the detection of the soluble pneumococcal antigen by counterimmunoelectrophoresis (Omnisernum of States Seruminstitut, Copenhagen, Denmark) and LP serogroup 1 antigen was determined by radioimmunoanalysis (Equate Legionella Urinary Antigen RIA; Binax, Portland, Ore).

The etiologic diagnosis of pneumonia by LP was achieved by the following: (1) isolation on respiratory samples (three cases); (2) a fourfold increase in antibody titers to 1:128 in the paired serum samples (34 cases); and/or (3) positive antigenemia (23 cases). In seven cases, the diagnosis of pneumonia by LP was established by several methods. One hundred twenty-five patients were diagnosed as having pneumonia of another etiology. The following diagnoses were established: (1) pneumococcal pneumonia in 68 cases by isolation of Streptococcus pneumoniae in blood culture (35 cases), pleural fluid (1 case), and/or detection of pneumococcal antigen in urine by counterimmunoelectrophoresis (41 cases); nine patients had more than one diagnostic test; (2) pneumonia by C pneumoniae in 41 cases by seroconversion at titers of IgG of ≥1:250; (3) M. pneumoniae (5 patients) by seroconversion; (4) C. burnetii (4 patients) by seroconversion; (5) Pseudomonas aeruginosa (3 patients); (6) Haemophilus influenzae (2 patients) by isolation in blood culture in both cases and Nocardia species by isolation in sputum culture. In the patients in this group, the serologic test results and/or the detection of the LP antigen in urine were negative.

**Variables Studied**

The following variables were studied: (1) demographic: age, sex; (2) risk factors: smoking; chronic alcoholism; underlying disease, including COPD, HIV infection, solid or hematologic neoplasms, diabetes mellitus, chronic liver disease, heart failure, chronic renal failure; pharmacologic immunosuppression (steroids and chemotherapy), splenectomy, IV drug addiction, and history of pneumonia within 1 year prior to hospital admission; (3) epidemiologic data: outbreak, recent hospitalization within the last 3 months, residence near excavations or construction work, contact with animals, birds, or recent journeys; (4) variables of clinical presentation: fever, cough, expectoration, thoracic pain, dyspnea, headache, confusion, abdominal pain, nausea or vomiting, diarrhea, arthromyalgia, days of evolution, and antibiotic treatment (β-lactam drugs and others) prior to the pneumonia and shock; (5) analytical data: leukocyte count, sodium (Na), creatine kinase (CK), aspartate aminotransferase (AST), BUN, and arterial gasometry while breathing room air (pH, PO2, Pco2, bicarbonate); and (6) radiologic presentation: unilateral or bilateral, monolobar or multilobar infiltrates, and alveolar or interstitial pattern determined by the same investigator.

**Definition of the Variables**: A patient was considered a smoker if he had smoked >1 pack/day within the last 5 years. Alcoholism was defined as consumption of >50 g of alcohol per day within the same period. Underlying diseases means presence of a comorbid illness. Steroidal use refers to treatment with >60 mg of prednisone per day over >2 weeks in the last month or >5 mg/d for more than the previous 3 weeks. Immunosuppression refers to treatment with cytopotic drugs not including steroid therapy.

**Statistical Methods**

Univariate analyses were performed using the Student’s t test for comparing quantitative variables and the χ2 test with/without Yates’ correction for qualitative variables by a statistical package (SAS; SAS Inc; Cary, NC) for personal computers. Variables with a level of 5% of significance in the univariate analysis or those considered of clinical importance, excluding collinear and dependent variables, were used in a multivariate logistic regression analysis carried out with software (SAS).

**Results**

**Demographic Characteristics and Risk Factors**

The demographic characteristics and risk factors of the two groups are presented in Table 1. The CAP by LP were found to be more frequent in male patients (85.4% vs 69.6%), in the 30- to 59-year-old group (56.2% vs 27.2%), in smokers (47.9% vs 33.6%), and in alcoholics (18.7% vs 4.8%). However, CAP by other bacterial etiology prevailed in the patients with underlying diseases (68.8% vs 41.6%) such as COPD (34.4% vs 16.7%), neoplasms (15.2% vs 4.2%), and HIV infection (20.8% vs 6.2%). All these variables except smoking and neoplasms were significant on univariate analysis. Moreover, history of pneumonia within 1 year prior to hospital admis-
Table 1—Demographic Variables and Risk Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAP-LP</th>
<th>Other CAP</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>(n=48)</td>
<td>(n=125)</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>2 (4.1)</td>
<td>24 (19.2)</td>
<td></td>
</tr>
<tr>
<td>30-59</td>
<td>27 (56.2)</td>
<td>34 (27.2)</td>
<td></td>
</tr>
<tr>
<td>&gt;59</td>
<td>9 (18.7)</td>
<td>6 (4.8)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>43 (85.4)</td>
<td>87 (69.6)</td>
<td>0.04†</td>
</tr>
<tr>
<td>Smoker</td>
<td>25 (51.0)</td>
<td>42 (33.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>9 (18.7)</td>
<td>6 (4.8)</td>
<td>0.006†</td>
</tr>
<tr>
<td>Underlying Disease</td>
<td>20 (41.6)</td>
<td>86 (68.8)</td>
<td>0.001†</td>
</tr>
<tr>
<td>COPD</td>
<td>8 (16.7)</td>
<td>43 (34.4)</td>
<td>0.02†</td>
</tr>
<tr>
<td>HIV</td>
<td>3 (6.2)</td>
<td>26 (20.8)</td>
<td>0.02†</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>2 (4.2)</td>
<td>19 (15.2)</td>
<td>0.06†</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (8.3)</td>
<td>16 (12.8)</td>
<td>0.59</td>
</tr>
<tr>
<td>Liver disease</td>
<td>4 (8.3)</td>
<td>11 (8.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (2.1)</td>
<td>5 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>1 (2.1)</td>
<td>3 (2.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>IV drug addiction</td>
<td>0</td>
<td>3 (2.4)</td>
<td>0.56</td>
</tr>
<tr>
<td>Steroid use</td>
<td>4 (8.3)</td>
<td>8 (6.4)</td>
<td>0.74</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>2 (4.2)</td>
<td>5 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous pneumonia</td>
<td>2 (4.2)</td>
<td>22 (17.4)</td>
<td>0.02†</td>
</tr>
</tbody>
</table>

*Statistical significance on univariate analysis.
†Significant variables.

Table 2—Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>p Value</th>
<th>OR*</th>
<th>CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.6306</td>
<td>1.123</td>
<td>0.701-1.798</td>
</tr>
<tr>
<td>Sex</td>
<td>0.9190</td>
<td>1.067</td>
<td>0.305-3.737</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>0.0118</td>
<td>0.223</td>
<td>0.069-0.717</td>
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<tr>
<td>β-Lactams</td>
<td>0.2079</td>
<td>2.299</td>
<td>0.629-8.400</td>
</tr>
<tr>
<td>Cough</td>
<td>0.1386</td>
<td>0.303</td>
<td>0.062-1.472</td>
</tr>
<tr>
<td>Expectoration</td>
<td>0.5170</td>
<td>1.574</td>
<td>0.399-6.209</td>
</tr>
<tr>
<td>Thoracic pain</td>
<td>0.6076</td>
<td>0.741</td>
<td>0.236-2.324</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.0101</td>
<td>5.793</td>
<td>1.320-22.077</td>
</tr>
<tr>
<td>Headache</td>
<td>0.4357</td>
<td>1.617</td>
<td>0.483-5.410</td>
</tr>
<tr>
<td>Na &lt;130 mmol/L</td>
<td>0.1703</td>
<td>3.022</td>
<td>0.622-14.685</td>
</tr>
<tr>
<td>CK &gt;232 U/L</td>
<td>0.0166</td>
<td>5.770</td>
<td>1.563-22.143</td>
</tr>
<tr>
<td>AST &gt;37 U/L</td>
<td>0.5400</td>
<td>0.608</td>
<td>0.221-2.207</td>
</tr>
</tbody>
</table>

*OR=odds ratio; CI=confidence interval.

Discussion

sion was significantly more frequent in the patients with CAP by other bacteria (17.4% vs 4.2%) in the univariate analysis. However, only underlying disease remained significant on multivariate analysis (Table 2).

Epidemiologic Characteristics

The cases of CAP by LP occurred sporadically throughout the year, contrary to the cases of CAP of other etiology that predominated in cold months (Fig 1). No seasonal predominance was observed in the cases of CAP by LP. History of recent hospitalization or hospital stay as an accompanying person was the only most frequent epidemiologic variable in CAP by LP (10/48 vs 13/125 cases), although this was not statistically significant on univariate analysis (p=0.07).

Clinical Presentation

The variables related to clinical presentation are shown in Table 3. The patients with CAP by bacteria other than LP had cough (89.6% vs 68.7%), expectoration (69.6% vs 41.7%), and thoracic pain (42.4% vs 25%) more frequently than those with CAP by LP. However, the patients with CAP by LP had a greater incidence of headache (29.2% vs 13.6%), confusion (20.8% vs 9.6%), and diarrhea (25% vs 64%). Likewise, the number of patients who had undergone β-lactam antibiotic treatment prior to hospital admission was also greater (31.1% vs 13.9%) than the group with CAP by LP. All these variables, except confusion, were significant on univariate analysis. However, only diarrhea remained significant on multivariate analysis (Table 2).

Laboratory Data

The analytical variables studied are shown in Table 3. The patients with CAP by LP demonstrated Na <130 mmol/L (28.9% vs 6.5%), elevation in AST level (60% vs 42.9%) and in CK level (32.3% vs 11.5%) more frequently than those with CAP by other bacterial etiology. However, only severe hyponatremia and elevation in CK level were statistically significant on univariate analysis, the latter remaining significant on multivariate analysis (Table 2).

Radiologic Presentation

Patients with CAP by LP had abnormal chest radiograph on presentation with alveolar (100%), unilateral (79.2%), and unilateral (85%) infiltrates in most of the cases. Patients with CAP by other etiology had also usually alveolar (97.6%), unilateral (79%), and unilateral (83.2%) infiltrates. Furthermore, 6 patients with CAP by LP (12.5%) and 20 with CAP by other bacterial etiology (16.8%) had pleural effusion at hospital admission. However, no significant differences were observed in the radiologic presentation between the two groups.

Discussion

The incidence of LP as a cause of CAP varies from 1 to 30%, depending on regional differences, the diagnostic methods used, and the range of the study. The greatest incidence is found in hospital series including patients with underlying disease and more severe pneumonia. In most studies, LP is consid-
would be considered as the third-highest cause of CAP\textsuperscript{1,5} and the second-highest cause of severe pneumonia.\textsuperscript{6-9} In our series of 392 cases of CAP, LP was the third-highest cause of CAP (12.5\%) after \textit{S. pneumoniae} (24\%) and \textit{C. pneumoniae} (13.5\%). Likewise, 20.4\% of CAP by LP required admission in the ICU vs 11.8\% of pneumococcal pneumonia and 6.8\% of the other bacterial CAP.\textsuperscript{21}

The high prevalence of LP as a cause of CAP in patients who are admitted to hospital, its greater severity, and the need for early initiation of antibiotic treatment to improve its prognosis\textsuperscript{9-13} make early diagnosis of the disease necessary. The routine use of rapid diagnostic techniques such as direct immunofluorescence of sputum and, more recently, the detection of the Legionella antigen in urine\textsuperscript{22,23} are not available in all centers given their high cost and technical difficulties. Thus, clinical, biological, and radiologic data that are sufficiently discriminatory would be of great help, particularly in the emergency department, at least in suspecting this etiologic diagnosis. Comparative studies are scarce and report contradictory results.\textsuperscript{15-19} The retrospective nature,\textsuperscript{15-17} low number of patients,\textsuperscript{15,16,18} and comparison with specific etiologies not representative of the etiologic spectrum of the CAP\textsuperscript{16-18} are, altogether, some of the problems that make evaluation of the results difficult. The present prospective study compares an elevated number of patients with other representative and most frequent bacterial etiologies in our area.

Epidemiologic studies have shown that elderly, male patients who smoke, and those with underlying diseases including diabetes, COPD, malignancy, renal diseases, and AIDS, have an elevated risk of acquiring Legionnaire’s disease.\textsuperscript{24} In our comparative study, previously healthy, drinking, middle-aged men predominated in the group with CAP by LP, while those with underlying diseases such as COPD and HIV infection were more frequently found to have CAP by other bacterial etiology. The greater incidence of underlying diseases, especially COPD and HIV infection, coincides in this group with the predisposition of these patients to acquire pneumococcal disease, as shown in previous studies.\textsuperscript{25} However, the diagnosis of CAP by LP in 3 of the 29 patients with HIV studied should lead to this etiology being considered in the differential diagnosis of pneumonias in this group.\textsuperscript{26} The patients with CAP by other bacterial etiology had pneumonia within 1 year prior to hospital admission significantly more often than those with CAP by LP, possibly due to the greater incidence of underlying diseases in this context.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{seasonal_distribution_of_cases.png}
\caption{Seasonal distribution of cases of pneumonia.}
\end{figure}
In this study, CAP by LP occurred sporadically, as observed in other studies,27,28 and contrary to the observations of other authors,12,17,24 no evident seasonal predominance was observed in our group with CAP by LP. No epidemiologic data were found to be associated with CAP by LP. The greater incidence of hospitalization in the previous 3 months or hospital stay as an accompanying person in this group coincides with the existence of an endemic situation of legionellosis in our hospital. Nevertheless, we were unable to demonstrate that the infection was nosocomial acquired. Moreover, patients who were hospitalized within the previous 10 days before the onset of symptoms of pneumonia were excluded.

After the first descriptions of LP, some clinical manifestations such as slight nonproductive cough, GI and neurological symptoms, failure to respond to β-lactam antibiotics, hyponatremia, and rhabdomyolysis were reported as suggestive of LP. Nevertheless, several comparative studies of CAP by LP and CAP by other bacterial etiology have shown very few differences in clinical presentation.15-18 In our study, diarrhea and headache were significantly more frequent in the group with CAP by LP. However, only diarrhea remained statistically significant on multivariate analysis. Fever, dyspnea, confusion, arthralgia, and other GI symptoms were not significantly associated with CAP by LP, contrary to other reports.3,11,15,18 However, cough, expectoration, and thoracic pain were associated with CAP by other bacterial etiology. The predominance of pneumococcal pneumonia in this group may explain this fact.17 Similar to those in other studies,3,18 patients with CAP by LP had undergone β-lactam antibiotic treatment with no improvement more frequently than patients with CAP by other bacterial etiology. The fact that more than one third of CAP in this group were caused by other bacteria such as C. pneumoniae, with an expected treatment response similar to CAP by LP, would have emphasized the significance of these data. However, contrary to other authors,14 no differences were found regarding the length of symptoms prior to hospital admission between both groups.

In our study, the analytical data associated with CAP by LP were severe hyponatremia (Na<130 mmol/L) and a moderate elevation of serum CK levels, similar to other reports.3,15,16 The elevation of CK level was the only variable showing significance on multivariate analysis. Rhabdomyolysis is infrequent in bacterial lung infection.29 Literature referring to the association of rhabdomyolysis with pneumonia by LP30,31 is scarce. However, minor elevations of CK levels have been described in some studies of pneumonia by LP.12,32

Finally, as reported by other authors,33 the radiologic presentation was similar in the two groups. Based on the results obtained in our study, it may be concluded that only diarrhea and elevation of CK level are significantly discriminatory of CAP by LP, but their sensitivity is very low. However, the combination of the demographic data, risk factors and clinical and analytical features of presentation that were significant in the univariate analysis, although lacking individual specificity, may aid in the early suspicion of CAP by LP in the emergency department. In this context, we believe that a macrolide with or without β-lactam drug, should be seriously considered as empiric treatment, and a rapid confirmatory test, such as antigen detection in urine, must be performed whenever possible.

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REFERENCES


Clinical Investigations