Nonsevere Community-Acquired Pneumonia
Correlation Between Cause and Severity or Comorbidity

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Background: Community-acquired pneumonia frequently constitutes a nonsevere infection manageable at home. However, for these low-risk episodes, the epidemiological features have not been carefully analyzed.

Objectives: To determine the cause of nonsevere community-acquired pneumonia and to investigate if a correlation exists between cause and severity or comorbidity.

Methods: During a 3-year period, all patients with nonsevere community-acquired pneumonia, according to the Pneumonia Patient Outcome Research Team prognostic classification (patients in groups 1-3), were included in the study. Causes were investigated through the following procedures: cultures of blood, sputum, and pleural fluid; serologic tests; and polymerase chain reaction methods to detect Streptococcus pneumoniae DNA in whole blood or Mycoplasma pneumoniae and Chlamydia pneumoniae DNA in throat swab specimens.

Results: Of 317 initially included patients, 247 were eligible for the study. A microbial diagnosis was obtained in 162 patients (66%), and the main pathogens detected were S pneumoniae (69 patients [28%]), M pneumoniae (40 patients [16%]), and C pneumoniae (28 patients [11%]). For the 58 patients in prognostic group 1, M pneumoniae was the most prevalent cause, and atypical microorganisms constituted 40 (69%) of the isolated agents. In contrast, for patients in prognostic groups 2 and 3, S pneumoniae was the leading agent, and a significant reduction of M pneumoniae cases and a greater presence of other more uncommon pathogens were observed. The existence of comorbid conditions was not a determining factor for particular causes.

Conclusions: Among low-risk patients with community-acquired pneumonia, there was a certain correlation between severity and cause. In contrast, the existence of a comorbidity did not have a predictive causative value.

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IT IS USUAL to state that community-acquired pneumonia (CAP) is responsible for considerable morbidity and mortality; however, many patients with this infection certainly have a nonsevere illness. Several studies have sought risk factors for the severity of pneumonia, and, actually, low-risk patients with CAP can be reasonably well identified. Fine et al1 recently developed and validated one of the most interesting risk classification systems, the Pneumonia Patient Outcome Research Team (Pneumonia PORT) prediction rule, to detect patients with nonsevere infection, based on age, sex, physical findings at hospital admission, the presence of selected coexisting illnesses, and some laboratory and radiographic results. Accordingly, patients are stratified into 5 categories with respect to the risk of death within 30 days, and those classified into groups 1 to 3 (a score of ≤90) constitute the low-risk group, a relatively homogeneous subset of patients because they have an overall good prognosis and can be managed at home, immediately or after a short hospitalization. This prognostic prediction rule has been widely accepted and has become a valuable tool for clinicians.2–4

Simultaneously, during the past decade, several guidelines5–7 for the diagnostic and therapeutic management of patients with CAP have been published. These guidelines also stratify patients according to age, severity of the clinical picture, and existence of a comorbidity. Therefore, a distinction between ambulatory and hospitalized populations is sug-
**PATIENTS AND METHODS**

On March 1, 1997, the Pneumonia PORT prognostic rule was incorporated into the management of CAP at our institution (a 500-bed university hospital in Catalonia, Spain). Simultaneously, we designed a prospective study to determine the cause of infection in those patients with low-risk infection.

**STUDY POPULATION**

During a 3-year period, demographic and clinical data at presentation from all adult patients (aged ≥18 years) admitted to the emergency department with a clinical and radiological image suggestive of CAP were analyzed, and the score, according to the prognostic rule, was calculated. For patients assigned to risk categories 2 to 5, laboratory tests were also performed. Finally, those patients assigned to categories 1 to 3 constituted the study group, and they were microbiologically studied through the further described methods. Informed consent was obtained from the patients, and the study was approved by the ethical and the scientific committees of our institution.

The presence of the following comorbid conditions was also determined by patient report and medical record review: chronic pulmonary diseases (chronic obstructive pulmonary disease, interstitial lung disease, or bronchiectasis), cardiovascular diseases (congestive heart failure or advanced ischemic heart disease), chronic hepatitis and hepatocellular diseases, recent or active neoplastic diseases, chronic renal insufficiency, diabetes mellitus, and cerebrovascular diseases with significant neurologic residual effects. In fact, many of these comorbidities were already identified as influencing factors in the Pneumonia PORT prognostic classification. According to the criteria used by Fine et al., patients with severe immunosuppression, patients who had been hospitalized in the previous 15 days, and patients known to have the human immunodeficiency virus infection were excluded.

**COLLECTION OF MICROBIOLOGICAL SPECIMENS**

The following battery of samples was obtained from patients:

1. Two blood specimens, for aerobic and anaerobic conventional cultures.
2. A considerable effort was made to obtain a good sputum sample. This was microscopically assessed to confirm its quality and, if alright, it was examined according to conventional methods. Sputum was also stained and cultured for *Mycobacterium* species or opportunistic pathogens only when it was indicated.
3. When present, pleural fluid was biochemically examined and processed for aerobic and anaerobic cultures.
4. An additional blood sample was obtained for *Streptococcus pneumoniae* DNA detection by polymerase chain reaction (PCR).
5. Since January 1, 1999, a throat swab sample was also collected and processed for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* genome detection by PCR.
6. Based on clinical suspicion, a urine sample for *Legionella pneumophila* antigen detection was processed.
7. Finally, a serum sample for serologic investigations was obtained, stored at −70°C, and reserved. Within 4 to 6 weeks of follow-up, a second serum sample was collected and processed with the first one to detect *M pneumoniae* (immunofluorescence test), *C pneumoniae* and *Chlamydia psittaci* (microimmunofluorescence test), *Coxiella burnetii* (complement fixation test), and *L pneumophila* (immunofluorescence test) antibodies.

**PCR METHODS**

The PCR technique was used to detect the *S pneumoniae* genome in whole blood and *M pneumoniae* and *C pneumoniae* in throat swab samples.

For the extraction of *S pneumoniae* DNA, 200 μL of whole blood samples was processed by using a kit (QIAamp Blood Kit; QIAgen, Hilden, Germany). We used the nested PCR methods.

Continued on next page

**RESULTS**

**PATIENT CHARACTERISTICS**

From a total of 317 patients with potential nonsevere CAP eligible for the study, 70 were excluded for several reasons: misdiagnosis at hospital admission (n=38), diagnosis of human immunodeficiency virus infection (n=16), error in the Pneumonia PORT rule application (n=13), or absence of informed consent (n=3). Thus, 247 patients constituted the final study group. The Pneumonia PORT prognostic score stratified patients as follows: 80 (32%) were included in class 1, 75 (30%) in class 2 (mean of score value, 56), and 92 (37%) in class 3 (mean of score value, 78) (percentages do not total 100 because of rounding).

The main epidemiological characteristics at hospital admission, for the overall population and for each prog-
Table 1

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Detection Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>S pneumoniae</td>
<td>PCR</td>
</tr>
<tr>
<td>C pneumoniae</td>
<td>PCR</td>
</tr>
<tr>
<td>M pneumoniae</td>
<td>PCR</td>
</tr>
</tbody>
</table>

Diagnostic Yield of Different Techniques

Blood samples for culture were obtained from 238 (96%) patients and gave positive results in 13 (5%), yielding S pneumoniae in 11, Streptococcus viridans in 1, and Staphylococcus aureus in 1. Bacteremia rates were 1% (1 of 78 patients), 7% (5 of 72 patients), and 8% (7 of 88 patients) for those in groups 1, 2, and 3, respectively. A blood sample for pneumococcal DNA detection by PCR was collected from 193 (78%) of 247 patients, and it was positive for S pneumoniae in 56. Pleural fluid, recovered from 22 (9%) of 238 patients, showed the presence of a respiratory pathogen by culture in 15 (S pneumoniae, 9; Haemophilus influenzae, 3; S viridans, 1; Enterococcus faecium, 1; and Mycobacterium tuberculosis, 1). Finally, a sputum sample for gram stain and culture was collected from 83 (35%) patients, of whom 66 provided a valid sample, and a significant microorganism was isolated in 14 (S pneumoniae, 6; H influenzae, 3; M tuberculosis, 3; and Pseudomonas aeruginosa, 2).

The first serologic sample was taken from 211 (85%) patients, and the second from 166 (67%), and the diagnosis by serologic analysis was made in 90 (M pneumoniae, 40; C pneumoniae, 26; C burnetii, 17; L pneumophila, 5; and C psittaci, 3 [1 patient had >1 infection]). A throat swab sample for PCR analysis was obtained from 66 (27%) patients, allowing the detection of M pneumoniae DNA in 1 patient and C pneumoniae DNA in 4 patients. Finally, 86 (35%) urine samples were analyzed for Legionella antigen detection, and the test result was positive in 6.
For patients with pneumococcal pneumonia, there was a good correlation between positive culture results and PCR results, as can be seen in Table 2. Thus, we detected \textit{S pneumoniae} DNA in the blood of 8 of 10 patients with bacteremia, 6 of 9 with positive pleural fluid culture results, and 2 of 5 with positive sputum culture results. Conversely, many patients with sterile culture results showed a positive PCR test result in blood. In contrast, for \textit{M pneumoniae} and \textit{C pneumoniae}, throat swab assays had, compared with serologic tests, reduced sensitivities (Table 3). Thus, only 1 throat swab specimen from 6 patients with \textit{M pneumoniae} infection, serologically diagnosed, and 2 from 4 patients with \textit{C pneumoniae} infection, with positive serologic test results, were positive by PCR; in addition, 2 cases of \textit{C pneumoniae} infection positive by PCR and negative by serologic test result were found.

In summary, a microbial diagnosis was made in 162 (66%) of the 247 patients: 138 had a definite diagnosis, while 24 had only a probable diagnosis. As Table 4 shows, \textit{S pneumoniae} (n=69), \textit{M pneumoniae} (n=40), and \textit{C pneumoniae} (n=28) were the most prevalent microorganisms. A mixed infection was detected in 17 (7%) patients.

**Table 1. Baseline Characteristics of the Patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group 1 (n = 80)</th>
<th>Group 2 (n = 75)</th>
<th>Group 3 (n = 92)</th>
<th>Total (N = 247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y†‡</td>
<td>32 (52)</td>
<td>52 (67)</td>
<td>67 (50)</td>
<td>32 (52)</td>
</tr>
<tr>
<td>Male-female ratio†‡</td>
<td>38:42</td>
<td>42:33</td>
<td>62:30</td>
<td>142:105</td>
</tr>
<tr>
<td>Smoking habit†‡</td>
<td>29 (36)</td>
<td>24 (32)</td>
<td>13 (14)</td>
<td>66 (27)</td>
</tr>
<tr>
<td>Alcohol abuse†‡</td>
<td>4 (5)</td>
<td>10 (13)</td>
<td>11 (12)</td>
<td>25 (10)</td>
</tr>
<tr>
<td>Comorbidity†‡</td>
<td>3 (4)</td>
<td>16 (21)</td>
<td>47 (51)</td>
<td>64 (26)§</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>0 (3)</td>
<td>3 (20)</td>
<td>20 (23)</td>
<td>23 (13)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (7)</td>
<td>4 (14)</td>
<td>14 (19)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Chronic pulmonary diseases</td>
<td>1 (7)</td>
<td>11 (11)</td>
<td>11 (11)</td>
<td>19 (12)</td>
</tr>
<tr>
<td>Hepatocellular diseases</td>
<td>0 (1)</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Cerebrovascular diseases</td>
<td>0 (1)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>0 (1)</td>
<td>1 (0)</td>
<td>0 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Prior antibiotic treatment‡</td>
<td>35 (44)</td>
<td>26 (35)</td>
<td>23 (25)</td>
<td>84 (34)</td>
</tr>
<tr>
<td>Pleural effusion‡</td>
<td>3 (4)</td>
<td>8 (11)</td>
<td>11 (12)</td>
<td>22 (9)</td>
</tr>
</tbody>
</table>

*Data are given as number of patients unless otherwise indicated.
†P < .05 (for the comparison of groups 1, 2, and 3).
‡Data are given as number (percentage) of patients.
§Some patients had more than 1 comorbidity.

**Table 2. Comparison Between PCR Results in Blood and Culture Results for Patients With Pneumococcal Pneumonia**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Culture Result</th>
<th>Blood PCR Result</th>
<th>Pleural fluid (n = 15)</th>
<th>Sputum (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Positive (n = 10)</td>
<td>Positive (n = 5)</td>
</tr>
<tr>
<td>Blood (n = 64)</td>
<td>8</td>
<td>2</td>
<td>48</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td></td>
<td>6 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td></td>
<td></td>
<td>6 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Sputum (n = 23)</td>
<td></td>
<td></td>
<td>2 (3)</td>
<td>16 (2)</td>
</tr>
</tbody>
</table>

*PCR indicates polymerase chain reaction.

**Table 3. Comparison Between PCR Results in Throat Swab Samples and Serologic Test Results for Patients With Pneumonia Caused by Mycoplasma pneumoniae and Chlamydia pneumoniae**

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Serologic Test Result</th>
<th>Throat Swab PCR Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycoplasma pneumoniae (n = 6)</td>
<td>Positive (n = 6)</td>
<td>Positive (n = 6)</td>
</tr>
<tr>
<td></td>
<td>Negative (n = 0)</td>
<td>Negative (n = 0)</td>
</tr>
<tr>
<td>Chlamydia pneumoniae (n = 6)</td>
<td>Positive (n = 4)</td>
<td>Positive (n = 2)</td>
</tr>
<tr>
<td></td>
<td>Negative (n = 2)</td>
<td>Negative (n = 0)</td>
</tr>
</tbody>
</table>

*PCR indicates polymerase chain reaction.

**DISTRIBUTION OF PATHOGENS BY PROGNOSTIC GROUPS**

Among the 80 patients included in prognostic group 1, a causative diagnosis was established in 56 (70%). As Table 5 shows, \textit{M pneumoniae} was the most frequent microorganism, identified as the causative agent in 23 patients; in addition, other atypical pathogens (\textit{C pneumoniae}, \textit{C burnetii}, and \textit{C psittaci}) also constituted relatively frequent causes. Therefore, excluding tuberculosis, some atypical agent was detected in 69% of the causatively diagnosed patients. Among conventional bacteria, only \textit{S pneumoniae} was detected with a significant frequency, and it was isolated in 16 patients. All patients who had tuberculosis were included in this prognostic category.

The microbial study of patients in prognostic groups 2 and 3 showed, in relation to group 1, a different pattern. A causative diagnosis was achieved in 55% (41/75) of the patients in group 2 and in 71% (65/92) of the patients in group 3. For both groups, the importance of \textit{S pneumoniae} notably increased, and it became the most frequently isolated microorganism, responsible for 21 and 32 cases among patients from groups 2 and 3, respec-
matically. In contrast, the incidence of pneumonia caused by M pneumoniae was reduced to 7 and 10 cases, respectively. We also observed in these groups (Table 5) an increasing presence of cases due to other atypical (L pneumophila) or conventional (P aeruginosa or several gram-positive cocci) bacteria. In general, the causative distribution of pathogens in groups 2 and 3 does not appear to be differential.

**IMPACT OF COMORBIDITY ON MICROBIAL CAUSE**

The existence of a comorbidity was not a useful discriminant variable for patients, as can be seen in Table 6. Thus, for both groups, either conventional or atypical bacteria constituted about 50% of the determined causative agents. Special mention merits the 7 cases of pneumonia caused by L pneumophila: all these patients did not have underlying disease and were younger than 50 years (mean age, 34 years; age range, 18-46 years), however, all were included into groups 2 (n=4) and 3 (n=3) because of the presence of clinical signs of severity.

In the present study, we examined many patients with nonsevere CAP, and the cause of pneumonia could be established in about 66% of the episodes. Mycoplasma pneumoniae and other atypical bacteria were the predominant microorganisms for patients with milder episodes, while S pneumoniae was the most prevalent pathogen among patients with a more severe infection, although atypical agents played an important role too. We also found that the presence of comorbid conditions did not influence the causative pattern.

Despite the fact that nonsevere episodes of CAP represent more than 50% of overall cases, they had previously received little attention from investigators and the epidemiological features remained not well recognized. So, therapeutic recommendations for empirical antibiotic therapy of these episodes mainly derived from epidemiological data obtained from hospitalized patients. Macfarlane found, in a retrospective review published in 1994, only 12 studies performed on ambulatory patients with CAP and, more recently, the experience in this field has not significantly increased. Moreover, populations analyzed in these reports were not homogeneous, because included together were ambulatory and hospitalized patients, in some reports, or patients with CAP and patients with other infections of the lower respiratory tract, in other reports. Also, the methods used to diagnose infection were frequently incomplete and, in many studies, only serologic tests were used; therefore, they undoubtedly underestimated the relative importance of bacterial infections. We can
conclude that more well-designed studies on low-risk patients with CAP, with emphasis on bacterial and atypical causes, are needed.

Substantial progress, related to the prognostic classification and the microbiological testing of patients with CAP, has been achieved over recent years, supporting the development of better-performed studies. Thus, with the publication of the Pneumonia PORT prognostic rule, specifically addressed to detect low-risk patients, episodes of nonsevere CAP have been clearly defined; therefore, uniform subsets of patients for study can be established. On the other hand, the availability of novel and more sensitive microbiological tests, such as genome or antigen detection methods, allows the identification of the responsible pathogen in more patients.

We know that serologic tests are sufficiently sensitive to detect infections caused by atypical pathogens. In fact, serologic tests have been shown to be more sensitive than cultures. In addition, novel diagnostic methods provide earlier results, but the sensitivity does not appear to be increased. However, to diagnose bacterial pneumonias, particularly those due to Staphylococcus pneumoniae, available conventional testing is imperfect. Blood and pleural fluid cultures provide only a reduced rate of positive results, and the utility of sputum gram stain and culture, when available, remains controversial because of the influence of sample quality on results. Studies have demonstrated that these classical diagnostic methods are even more poorly contributive to diagnosis in patients with milder infection.

Therefore, we used, in association with traditional techniques, PCR tests in determining the causative diagnosis. Our experience supports results derived from a previous report, in which the nested PCR technique, applied to whole blood samples and compared with an extensive battery of alternative diagnostic methods, had a good sensitivity and a high specificity for diagnosing pneumococcal pneumonia. Similarly, favorable results of the method have also been reported by others. On the other hand, promising results have been reported with the application of PCR analysis in throat swab samples for the detection of M pneumoniae or C pneumoniae infection, becoming, for both microorganisms, a useful diagnostic method with clinical application. However, in our study, PCR analysis for M pneumoniae and C pneumoniae appeared to be insensitive, and the method was mildly contributive to the diagnosis. We believe that a possible explanation for this discrepancy could be based on technical characteristics; certainly, the nested PCR test has shown to be more sensitive than the single-step PCR, the method that we used for these 2 agents. Alternatively, we also could speculate about the relative nonspecificity of some serologic data; however, our limited experience does not allow us to evaluate this possibility.

We hope that our results provide valuable and practical implications in the management of low-risk patients with CAP, and, undoubtedly, the understanding of the pathogens most frequently involved is a key consideration in the choice of empirical antibiotic therapy. Thus, we found, among patients in group 1, a clear predominance of atypical pathogens, causing about 70% of the cases; M pneumoniae was the most prevalent microorganism. This finding is consistent with the results of previous articles; in fact, M pneumoniae has traditionally been associated with a young and previously healthy population with CAP. Conversely, S pneumoniae, which appears as the most frequent causative pathogen for outpatient in significant guidelines, had a proportionally more reduced relevance.

For patients in prognostic groups 2 and 3, the microbial spectrum of CAP was more diverse, and we found epidemiological features similar to those found in present studies of hospital-based populations. Certainly, S pneumoniae was the most prevalent individual cause; however, the atypical group of microorganisms was encountered in almost 50% of the cases. In addition, other more uncommon agents appeared also as potential causative pathogens; thus, we detected some cases of L pneumonia or episodes caused by other conventional bacteria (S aureus, S viridans, or even gram-negative bacilli). Interestingly, both groups showed a similar causative pattern. On the other hand, among patients included in these prognostic groups, we also found, in relation to patients in group 1, higher levels of bacteremia, although the difference did not reach statistical significance, probably due to the reduced number of bacteremic episodes. Finally, the existence of underlying diseases was not associated with any discernible microbial cause.

The present study has several limitations. First, it was developed using patients who had been seen at the hospital. Certainly, the application of a classification rule would theoretically have to provide homogeneous groups; however, particularly among group 1 patients, we cannot exclude that many of those with mild episodes did not reach the hospital. Therefore, they may be underrepresented in our study. This potential bias exists, but, in Spain, many patients seek medical care directly from the emergency service of the hospital rather than after a visit to a primary care physician. In addition, as done by Fine et al, human immunodeficiency virus–infected patients were explicitly excluded in our study; we know from previous reports that this population shows a distinct causative pattern, with a predominance for bacterial pathogens, even among those with less severe manifestations of disease.

On the other hand, we were not uniformly aggressive in conducting the causative investigations, with a proportionally reduced use of diagnostic methods to detect some more improbable causative agents, such as H influenzae or gram-negative bacilli, and a limitation to conventional tests. Thus, we cannot exclude that these microorganisms may have been underestimated in the present study; however, we have evidence that the relevance of these more unusual pathogens, particularly among nonsevere cases of pneumonia, is truly low. In addition, microbiological studies to detect viral infections were not routinely performed. Certainly, the pathogenic role of respiratory viruses in adult patients with CAP is a controversial field and, frequently, they are detected in patients with mixed infections, coexisting with another bacterial cause. However, it is also possible that a proportion of these patients with an unknown cause had definite viral pneumonia.
In summary, CAP constitutes, for Pneumonia PORT prognostic group 1 patients, an infection commonly caused by atypical microorganisms. In contrast, for patients in Pneumonia PORT groups 2 and 3, the microbial spectrum is more varied, including, in a similar proportion, either bacterial or atypical agents. Furthermore, we were unable to establish associations between particular pathogens and the existence of underlying diseases.

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