Differences in the etiology of community-acquired pneumonia according to site of care: A population-based study

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Summary
Background: A few population-based studies assessing the etiology of community-acquired pneumonia in both hospitalized and ambulatory patients, with special emphasis

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Etiology of community-acquired pneumonia

Introduction

Most etiologic studies of community-acquired pneumonia in adults have been carried out in patients who were referred to the hospital for consultation or in those hospitalized for inpatient care. Little information is available on the microbiologic etiology of outpatients with community-acquired pneumonia. Moreover, a few population-based studies assessing the etiology of pneumonia in both hospitalized and ambulatory patients have been reported. In some of these studies, however, respiratory viruses have not been considered or it has been claimed that the etiology of ambulatory community-acquired pneumonia does not differ from that of severe pneumonia requiring hospitalization. This study was designed to compare the microbiological etiology of community-acquired pneumonia according to initial site of care, whether outpatient or in-hospital, with emphasis on the viral etiology, using data from three population-based studies carried out in the same geographical area with the same methodology over a 4-year period.

Materials and methods

Study population

All subjects > 14 years of age living in a pre-defined area of the “Maresme” region in the Mediterranean coast in Barcelona, Spain, with a definite diagnosis of community-acquired pneumonia were included. These patients were collected from the study samples of three population-based studies carried out between November 1987 and November 1995. All physicians working in public primary health care centers and private clinics of the “Maresme” region as well as the emergency services of public and private reference hospitals in the area participated in the reporting of cases.

All cases of clinically suspected community-acquired pneumonia were prospectively registered. Criteria for clinical suspicion of acute lower respiratory tract infection included the presence of three or more of the following manifestations: cough with or without sputum production, dyspnea and/or wheezing, pleuritic chest pain or abdominal pain, fever, headache, pulmonary consolidation on auscultation of the chest, sweating, arthralgias, dysphagia, and coryza. For clinically atypical community-acquired pneumonia, one or more of the following criteria were considered: sweating, arthralgias, dysphagia, and coryza that required antibiotic prescription or persisted > 5 days without antibiotics. In elderly patients, the possibility of pneumonia was also considered in the presence of prostration and/or anorexia and/or confusion or disorientation. In all cases in which criteria for clinical suspicion were met, a chest radiograph was ordered. Patients with initial doubtful radiographic images of community-acquired pneumonia were tentatively included in the study and then excluded or definitively included according to clinical evolution and subsequent roentgenographic findings. All cases of community-acquired pneumonia were re-evaluated by chest roentgenograms on the 5th day of illness and at monthly intervals until complete recovery.

Patients with aspiration pneumonia (witnessed aspiration with respiratory symptoms or oral content of aspiration) or active pulmonary tuberculosis, and patients coming from nursing homes or having been discharged from hospital at least within 7 days before the onset of symptoms were excluded.

Decisions about hospitalization were made according to the risk classes defined by Fine et al. The pneumonia severity index (PSI) was calculated in all hospitalized patients.
patients with pneumonia. The PSI in patients attended in the outpatient setting was not calculated due to unavailability of biochemical results (serum glucose, blood urea nitrogen, sodium) and hematocrit value.

For each individual population-based study, the Review Board of the reference hospital approved the study protocol. Informed consent was not obtained because no special intervention for the purpose of the study was performed and patients were treated according to standard care of daily practice.

Microbiological studies

In patients with fever $\geq 38^\circ$C, two blood cultures were drawn. When lower respiratory tract secretions (via fiberoptic bronchoscopy, bronchoalveolar lavage, plugged double catheter) or pleural fluid samples were obtained, these were cultured too. Paired serology, at the moment of diagnosis and within the 4–6th week were also collected. Sera were tested for evidence of complement fixing antibodies to influenza A and B; parainfluenza 1, 2, and 3; adenovirus; respiratory syncytial virus (RSV); Chlamydia psittaci; Coxiella burnetii, and Mycoplasma pneumoniae. The indirect fluorescent antibody technique was used for detecting immunoglobulin (IgG) against Legionella pneumophila serogroups 1–6. The indirect microimmunofluorescence antibody technique was used for detecting IgG and IgM against Chlamydia pneumoniae. When varicella pneumonia was suspected on the basis of clinical history and typical cutaneous lesions consistent with chickenpox, testing for antibodies was performed by standard complement-fixation technique.

Urine samples were also collected and frozen at $-30^\circ$C to perform the following tests in one batch towards the end of the studies: test for pneumococcal polysaccharide capsular antigen and Haemophilus influenzae type B capsular antigen. In order to minimize possible non-specific reactions, all urine samples were heated at 100°C for 3 min. Urine samples were centrifuged at 2000 $x$ g for 10 min and tests for antigen were performed in both concentrated and unconcentrated urine $\sim$20-fold by means of a disposable ultrafilter (Minicon-B15 concentrator Amicon, Beverly, MA, USA). H. influenzae type B capsular antigen was detected in urine with a commercially available latex kit (Bactigen, Wampole Laboratories, Cranbury, NJ, USA) according to the manufacturer’s instructions. Pneumococcal polysaccharide capsular antigen was detected in urine by counterimmunoelectrophoresis (CIE) with pneumococcal Ommiserum (Statens Serum Institut, Copenhagen, Denmark). In a subgroup of the last study,5 urine samples were also tested for L. pneumophila serogroup 1 antigen by ELISA.

Microbiological testing was always performed prior to the administration of antibiotics. An etiologic diagnosis was based on: (1) blood cultures yielding a bacterial or fungal pathogen (in the absence of an apparent extrapulmonary focus); (2) pleural fluid culture yielding a bacterial pathogen; (3) seroconversion, i.e., a four-fold rise in IgG-titers for C. pneumoniae (IgG $\geq 1:512$), M. pneumonia (IgG $\geq 1:80$), C. psittaci (IgG $\geq 1:64$), L. pneumophila (IgG $\geq 1:128$), C. burnetii (IgG $\geq 1:80$), respiratory viruses (influenza virus A and B, parainfluenzavirus 1–3, RSV, adenovirus), and a four-fold rise in Varicella-zoster virus antibodies; (4) a positive urinary antigen for Streptococcus pneumoniae polysaccharide capsular antigen, H. influenzae type B capsular antigen, and L. pneumophila serogroup 1 antigen; or (5) bronchoalveolar lavage cultures yielding $\geq 10^4$ colony-forming units (CFU) per milliliter, or protected specimen brush cultures yielding $\geq 10^3$ CFU mL$^{-1}$.

Results of sputum culture were not considered due to the low yield of this technique6,7 and the controversy in the interpretation of results as definite etiological agent of community-acquired pneumonia.2,8,11

Statistical analysis

The diagnostic yield of each microbiological technique was expressed as the number of patients with a positive result divided by the total number of patients submitted to the diagnostic test. For the comparison of percentages, differences according to site of care were assessed with the Chi-square ($\chi^2$) test or the Fisher’s exact test. The Statistical Package for the Social Sciences (SPSS, version 12.0) was used for the analysis of data. Statistical significance was set at $P < 0.05$.

Results

In 86 (14.7%) of the 582 patients initially included in the three population-based studies, the diagnosis of community-acquired pneumonia was not confirmed (non-pneumonic respiratory infection 36, pleural adhesions 10, lung cancer 13, atelectasis 13, acute pulmonary edema 7, lung abscess 4, chronic organized pneumonia 1, chronic vasculitis 1, and extrinsic allergic alveolitis 1). Therefore, the study population included 496 patients, 280 (56.5%) treated in the hospital and 216 (43.5%) treated at home. The characteristics of patients according to site of care are shown in Table 1. The mortality rate was 6.4% for inpatients vs. 1.4% for outpatients.

Of the 474 patients with etiological evaluation, 195 patients had an identifiable etiology, which resulted in an overall diagnostic yield of 41.1%. A total of 215 pathogens were identified, a single pathogen in 175 patients and two pathogens in 20 (Table 2). S. pneumoniae was the most common causative pathogen followed by C. pneumoniae and M. pneumoniae.

Viral etiology (influenza A, influenza B, parainfluenza virus, RSV, adenovirus, and varicella virus) was documented in 48 patients (24.6%), 39 of whom were admitted to the hospital and 9 were treated in the outpatient setting. In hospitalized patients, viral etiology accounted for 16.8% of all serological tests performed (39 out of 231), whereas in ambulatory patients, viral etiology accounted for 4.8% of all serological tests performed (9 out of 185). On the other hand, viral etiology was documented as a single pathogen in 33 patients, or in association with other organisms in 15 patients (75% of dual infections). As shown in Table 2, the diagnostic yield of invasive procedures with adequate sampling was 100% followed by serological tests (31.3%), pleural fluid culture (17.4%), urine antigen (13.5%), and blood culture (7%).
In the group of 280 inpatients, an etiologic diagnosis was made in 133 (47.5%), with a total of 147 pathogens identified. In the group of 216 outpatients, 62 (28.7%) had an identifiable etiology, with a total of 68 pathogens identified. Diagnostic techniques were different according to the site of care. As expected, culture of respiratory samples obtained by invasive procedures was only performed in hospitalized patients with a 100% diagnostic yield. Urine antigen testing and serological tests were performed more frequently among hospitalized patients, but differences compared with outpatient care were not statistically significant. Blood cultures were more often performed in the inpatient care than in the outpatient care setting (8.6% vs. 1.4%, \( P < 0.0001 \)). Diagnostic yield was consistently higher among inpatients than ambulatory patients for serological tests (35.5% vs. 25.9%, \( P = 0.04 \)), blood cultures (9.7% vs. 2.2%, \( P = 0.0006 \)), and urine antigens (16.7% vs. 9.6%, \( P = 0.04 \)) (Table 2).

Table 3 shows the etiology of community-acquired pneumonia according to site of care. In both groups, \( S. pneumoniae \) was the most common causative organism. Viral infection was diagnosed in 26.5% of hospitalized patients compared with 13.2% of ambulatory patients (\( P = 0.03 \)). There were no differences in the distribution of patients with viral pneumonia according to PSI classes (I–II, 23.3%; III, 20.8%; IV–V, 19.5%). On the other hand, the same distribution of cases of viral pneumonia was observed along the three study periods surveyed and no predominant seasonal distribution was recorded. Twenty-five percent of the 68 patients with documented etiology treated at home had \( C. pneumoniae \) infection compared with 14.3% of those treated in the hospital. \( M. pneumoniae \) and \( C. burnetii \) were more frequently identified in ambulatory patients. Pneumonia cause by \( Pneumocystis jiroveci \) was only documented in the hospitalized group.

A total of 10.5% of hospitalized patients had community-acquired pneumonia caused by two pathogens compared with 9.7% of patients treated at home. The most commonly involved pathogens in dual infections among hospitalized patients were viruses (\( n = 11 \)), \( S. pneumoniae \) (\( n = 7 \)), and \( C. pneumoniae \) (\( n = 6 \)). Viruses were identified in four ambulatory patients with community-acquired pneumonia caused by two pathogens, \( S. pneumoniae \) in three, and \( C. pneumoniae \) in three. The association of viruses and bacteria was the most frequent cause of dual infection (78.6% inpatients vs. 66.7% outpatients).

Discussion

Following pre-established criteria, 57.1% of patients were admitted to the hospital. There is a large variability across studies in relation to differences in strategies for admission decision, and a tendency to overestimate the severity of pneumonia.\(^{13}\) In our group of hospitalized patients, 34.6% belonged to PSI risk classes I and II, which is similar to the 31.1% reported in a multicenter study carried out in our country.\(^{13}\) Diagnostic yield was low, although consistent with data of other studies using similar procedures.\(^{14}\) Higher yield has been reported in studies that have included pathogens identified in sputum samples.\(^{15,16}\) When diagnostic yield according to the different procedures was assessed, results were consistently higher among inpatients than ambulatory patients.

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Table 1  Baseline characteristics of the study population by site of care.

<table>
<thead>
<tr>
<th>Data</th>
<th>Total (( n = 496 ))</th>
<th>Inpatients (( n = 280 ))</th>
<th>Outpatients (( n = 216 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, no. (%)</td>
<td>194 (39.1)</td>
<td>87 (31.1)</td>
<td>107 (49.6)</td>
</tr>
<tr>
<td>Age &lt;65 years, no. (%)</td>
<td>338 (68.1)</td>
<td>150 (53.6)</td>
<td>188 (87.0)</td>
</tr>
<tr>
<td>Age ≥65 years, no. (%)</td>
<td>158 (31.9)</td>
<td>130 (46.4)</td>
<td>28 (13.0)</td>
</tr>
<tr>
<td>Co-morbidity*, no. (%)</td>
<td>393 (79.2)</td>
<td>204 (72.9)</td>
<td>189 (87.5)</td>
</tr>
<tr>
<td>None</td>
<td>58 (11.7)</td>
<td>41 (14.6)</td>
<td>17 (7.9)</td>
</tr>
<tr>
<td>One underlying illness</td>
<td>45 (9.1)</td>
<td>35 (12.5)</td>
<td>10 (4.6)</td>
</tr>
<tr>
<td>Respiratory rate, mean (SD)</td>
<td>23 (8)</td>
<td>26 (8)</td>
<td>19 (4)</td>
</tr>
<tr>
<td>Temperature, (°C) mean (SD)</td>
<td>38 (1.0)</td>
<td>38.2 (0.9)</td>
<td>37.7 (0.9)</td>
</tr>
<tr>
<td>Multilobar pneumonia, no. (%)</td>
<td>29 (5.8)</td>
<td>28 (10)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Bilateral pneumonia, no. (%)</td>
<td>22 (4.4)</td>
<td>21 (7.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pleural effusion, no. (%)</td>
<td>39 (7.9)</td>
<td>38 (13.6)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Pneumonia severity index, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>33 (11.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>64 (22.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>66 (23.6)</td>
<td></td>
<td></td>
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<tr>
<td>Class IV</td>
<td>80 (28.6)</td>
<td></td>
<td></td>
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<tr>
<td>Class V</td>
<td>37 (13.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation.
*Diabetes mellitus, heart failure, bronchial asthma, chronic obstructive pulmonary disease, chronic bronchitis, epilepsy, Parkinson’s disease, neuromuscular diseases, swallowing disorders, dementia, chronic liver dysfunction, chronic renal insufficiency, cancer in remission.
The relationship between greater yield and severity of pneumonia has been already reported.16,17

*S. pneumoniae* was the most common pathogen in either inpatients or outpatients, which is in agreement with other studies.18 Viruses were the second most frequent causative agents. Although in studies in immunocompromised patients in whom herpes simplex virus was documented in 42% of cases and cytomegalovirus in 31%,19 in non-immunocompromised patients with community-acquired pneumonia, viral etiology as single or associated infection has been observed in 18–20% of patients admitted to the hospital.20,21 As single causative agent, viral infection has been recorded in 9% of hospitalized patients.20 In the present study, viral pneumonia was associated with a higher severity of illness. It was diagnosed in 26.5% of patients admitted to the hospital, 18.3% as single pathogen, whereas in patients treated at home these percentages were 14.5% and 8.1%, respectively. Similar findings were reported by Lagerström et al.22 with viral infection detected in 13.9% of ambulatory patients (single pathogen 33.3%, dual pathogen 66.7%). The inclusion of paired serological test in the diagnostic protocol may account for the high percentage of viral pneumonia observed in the present study. In fact, paired serological tests were performed in 231 of 280 inpatients and in 185 of 216 outpatients. Although these data do not possibly reflect routine daily practice, they are indicative of the role played by major respiratory viruses in the etiology of community-acquired pneumonia, which can be confirmed by the use of new diagnostic techniques of rapid viral detection, such as real-time polymerase chain reaction (PCR).23,24 The etiological role of viral infections in adult lower respiratory tract infection in the outpatient setting has been highlighted in a recent study,25 in which viruses accounted for 63% of infections with rhinoviruses being the most common

![Table 2](image)

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organisms. In this study, however, the diagnostic methodology was different from the current study. The authors employed PCR and reverse PCR technology and also sputum samples. In our study, the three patients with clinical manifestations suggestive of varicella were hospitalized and the etiological diagnosis was confirmed by serological test. Cases of mild community-acquired pneumonia caused by Varicella-zoster virus and treated at home are probably underdiagnosed if patients with this condition are not submitted to other diagnostic studies.

C. pneumoniae was the third more frequent etiologic agent among inpatients and the second most frequent pathogen among ambulatory patients. Interestingly, seven of eight patients with C. burnetii infection were treated as outpatients. C. burnetii is a relatively common cause of community-acquired pneumonia in some geographical areas and among people in contact with animals. Infection by L. pneumophila is uncommon in the community in the absence of outbreaks. However, L. pneumophila was the cause of community-acquired pneumonia in 4.1% of cases and despite the fact that this organism has been implicated with a greater severity of illness, in our study, 30% of patients were treated at home, which is consistent with the data reported by Carratala et al. Likewise, patients with M. pneumoniae were preferentially treated as outpatients. H. influenzae is a common etiology of community-acquired pneumonia in elderly patients and in patients with chronic obstructive pulmonary disease, but in the present study the diagnostic yield was low because results of sputum culture were not considered.

In this study, 10.4% of patients with etiological diagnosis had two pathogens identified. In 75% of these cases a viral agent was detected, which probably was the cause of bacterial superinfection. In agreement with the study of De Roux et al., viral agents in patients with dual infection occurred in association with S. pneumoniae or C. pneumoniae. Community-acquired pneumonia with more than one organism recovered is a challenging dilemma because it is difficult to assess the role of individual organisms in the pathogenesis of the disease. In some cases, the presence of both pathogens may contribute to the illness, although in other cases, infection by one pathogen may favor the second pathogen to be the cause of community-acquired pneumonia. Other studies have shown dual pathogens in 10–25% of cases, probably in relation to the diagnostic procedures used. In contrast, other authors considered that community-acquired pneumonia is caused by a single pathogen, the remaining organisms isolated representing colonization of the airways, and attributing co-infection to punctual cases, such as aspiration pneumonia or lung abscesses caused by anaerobes.

In a recent study covering the period from 1996 to 2001 assessing the incidence and principal microbial patterns of mixed community-acquired pneumonia in a Barcelona teaching hospital, the most frequent combination was S. pneumoniae and H. influenzae followed by influenza virus A and S. pneumoniae. In our study, the most commonly involved pathogens in dual infections among hospitalized patients were also viruses, S. pneumoniae and C. pneumoniae. In a 2-year prospective study of consecutive patients with community-acquired pneumonia carried out in Alicante (Spain), a single pathogen was detected in 45% cases and two or more pathogens in 5.7% cases. Mixed infections were seen across all age groups and in patients treated both in hospital and as outpatients. The most frequent combination of pathogens were those of a bacterium plus an "atypical" organism (28.6%) and of two bacterial organisms (28.6%). Patients with mixed pneumonia were more likely to have underlying medical conditions, and they may have a more severe course of disease.

Finally, the limitation of the method used to detect pneumococcal antigen in urine should be recognized. Novel
and more simple methods, such as immunochromatography technique for detecting urinary \textit{S. pneumoniae} antigen in the etiologic diagnosis of community-acquired pneumonias have been recently introduced. In a prospective study of 959 inpatients with community-acquired pneumonia in which urinary pneumococcal antigen content was determined in 911 using the immunochromatography assay, the percentage of diagnoses of pneumococcal pneumonias increased by 26\%, while the overall etiologic diagnosis increased from 28\% to 49\% compared with conventional microbiologic methods.\textsuperscript{34} The technique sensitivity was 81\%; the specificity oscillated between 80\% in community-acquired pneumonia with non-

pneumococcal etiology and 99\% for patients with fractures without infections. Determination of urine pneumococcal antigen is a rapid, simple analysis with good sensitivity and specificity, which increased the percentage of etiologic diagnoses. This study in which data provided come from three previous studies conducted from 1987 to 1995 has provided information on etiology of community-acquired pneumonia in hospitalized patients and in patients treated at home using population-based data from studies in a single region of Spain. A considerable proportion of patients had viral pneumonia, frequently requiring hospital admission for inpatient care.

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