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Clinical characterisation of pneumonia caused by atypical pathogens combining classic and novel predictors

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ABSTRACT

The aim of this study was to characterise community-acquired pneumonia (CAP) caused by atypical pathogens by combining distinctive clinical and epidemiological features and novel biological markers. A population-based prospective study of consecutive patients with CAP included investigation of biomarkers of bacterial infection, e.g., procalcitonin, C-reactive protein and lipopolysaccharide-binding protein (LBP) levels. Clinical, radiological and laboratory data for patients with CAP caused by atypical pathogens were compared by univariate and multivariate analysis with data for patients with typical pathogens and patients from whom no organisms were identified. Two predictive scoring models were developed with the most discriminatory variables from multivariate analysis. Of 493 patients, 94 had CAP caused by atypical pathogens. According to multivariate analysis, patients with atypical pneumonia were more likely to have normal white blood cell counts, have repetitive air-conditioning exposure, be aged <65 years, have elevated aspartate aminotransferase levels, have been exposed to birds, and have lower serum levels of LBP. Two different scoring systems were developed that predicted atypical pathogens with sensitivities of 35.2% and 48.8%, and specificities of 93% and 91%, respectively. The combination of selected patient characteristics and laboratory data identified up to half of the cases of atypical pneumonia with high specificity, which should help clinicians to optimise initial empirical therapy for CAP.

Keywords Atypical pneumonia, community-acquired pneumonia, diagnosis, identification, scoring models, variables

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INTRODUCTION

Selection of empirical therapy for community-acquired pneumonia (CAP) has become complicated by the marked increase in β-lactam and macrolide resistance among strains of *Streptococcus pneumoniae*, and by the concerns about atypical pathogens (e.g., *Mycoplasma pneumoniae*, *Chlamydophila* spp. and *Legionella* spp.) [1–6]. No general agreement currently exists concerning the selection of the antimicrobial regimen for all patient groups. UK guidelines for outpatients with non-severe pneumonia advocate initial therapy with amoxycillin (http://www.brit-thoracic.org/guidelines), despite the high frequency of atypical organisms [1–4]. In contrast, North American guidelines still recommend monotherapy with macrolides for many outpatients [5], which is an approach that can be questioned in view of the increasing rates of resistance among pneumococci [6]. In view of these uncertainties, clinicians may decide to provide empirical therapy targeted against both standard pathogens and atypical organisms for patients with CAP by prescribing combined therapy with a β-lactam and a macrolide, or monotherapy with a respiratory fluoroquinolone. Although initial empirical

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therapy for patients who require admission to hospital may require broad-spectrum coverage, overuse of antibiotics for all patients with CAP might lead to increasing drug resistance during the next few years [6,7].

Atypical organisms are now considered to be an important cause of CAP, being implicated in 20–40% of CAP cases [1–4]. Unfortunately, coverage of atypical pathogens remains empirical in most cases because of an absence of rapid, standardised diagnostic tests. Although molecular techniques, e.g., PCR with respiratory secretions, are promising [5], their accuracy and reproducibility have yet to be established, and no commercial assays are currently available for use by clinical microbiology laboratories. In this scenario, the availability of predictors of infection by atypical organisms would be of interest, since they could help determine the initial therapy for cases of CAP. However, epidemiological studies have shown that single clinical, radiological or laboratory parameters have limited value in predicting the microbial aetiology of CAP and in characterising atypical pneumonia [4,8–10].

Rapid diagnostic tests for bacterial pneumonia, e.g., the pneumococcal urinary antigen test [11], have become available recently, and novel serum biomarkers of bacterial infection, e.g., procalcitonin (PCT), have been described [12,13]. The information provided by these tests could be useful as additional criteria for differentiating between atypical and classical bacterial aetiology in CAP. The present study describes a large prospective investigation of CAP in which the clinical features of the patients were recorded, and extensive laboratory investigations, including determinations of pneumococcal urinary antigen and serum biomarkers of bacterial infection, were performed [14]. Three previous reports have evaluated the Binax immunochromatographic assay for detection of *S. pneumoniae* urinary antigen in the same patient cohort [15], together with the usefulness of lipopolysaccharide-binding protein (LBP) [16] and PCT [17] as predictors of aetiology and prognosis. The objective of the present study was to characterise atypical pneumonia by combining laboratory data with the epidemiological and clinical features of the patients. In addition, a scoring system was devised to compare CAP caused by atypical pathogens with other causes of CAP in order to determine the variables that were most effective in discriminating atypical pathogens from other organisms.

PATIENTS AND METHODS

Setting and population studied

This prospective study was conducted at Hospital General Universitario de Elche, a 430-bed university-affiliated teaching hospital serving a population of 250 000 in Alicante, a province on the Mediterranean coast of Spain. All adult patients (aged ≥15 years) with signs and symptoms compatible with pneumonia during two consecutive periods of 12 months (from 15 October 1999 to 14 October 2000, and from 15 October 2000 to 14 October 2001) were eligible for inclusion in the study. The study was approved by the local ethical committee, and informed consent was obtained from all the patients. CAP was defined as an acute illness associated with at least one of the following signs or symptoms: fever (measured by axillary temperature, which is common clinical practice in our centre); new cough, with or without sputum production; pleuritic chest pain; dyspnoea; and altered breath sound on auscultation, plus a chest radiograph showing an opacity compatible with the presence of acute pneumonia. Patients with a provisional diagnosis of CAP were seen within 48 h by a study investigator to confirm the diagnosis. Patients with previous hospitalisation within 2 weeks of the current diagnosis of pneumonia were excluded.

Demographical and clinical data were collected using a written standardised questionnaire. Among the clinical data, air-conditioning exposure was defined as repetitive and prolonged (several hours a day) exposure at home or at work, and exposure to birds was defined as having birds at home or at work, or frequent contact with birds as a hobby. The severity of pneumonia was calculated using the Pneumonia Patient Outcome Research Team (PORT) severity index (PSI) [18], which classifies patients, according to outcome, in five risk classes (class I includes patients with the most favourable prognosis, and class V those with the poorest prognosis). All patients were followed for at least 4 weeks or until death. A repeat chest radiograph and a blood sample were obtained 2–4 weeks after the initial diagnosis of CAP.

Microbiological investigations

The laboratory investigation for a patient with CAP has been described previously [14]. In brief, it included obtaining sputum samples for Gram's stain and culture, two blood samples for culture, a urine sample for detection of *Legionella pneumophila* and *S. pneumoniae* antigens, and serum samples for detection of antibodies against atypical pathogens and viruses (taken during the acute stage of illness and at least 2 weeks later).

A complement fixation test was performed to detect antibodies against *M. pneumoniae*, *Chlamydophila* spp., *Coxiella burnetii*, influenza viruses A and B, respiratory syncytial virus and adenovirus. An indirect immunofluorescence test was used to detect antibodies to *L. pneumophila*, and a microimmunofluorescence test was used to detect antibodies against *Chlamydophila pneumoniae*, *Chlamydophila psittaci* and *Chlamydophila trachomatis*.