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Community-acquired pneumonia: development of a bedside predictive model and scoring system to identify the aetiology

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Although initial presentation has been commonly used to select empirical therapy in patients with community-acquired pneumonia (CAP), few studies have provided a quantitative estimation of its value. The objective of this study was to analyse whether a combination of basic clinical and laboratory information performed at bedside can accurately predict the aetiology of pneumonia.

A prospective study was developed among patients admitted to the Emergency Department University Hospital Arnau de Vilanova, Lleida, Spain, with CAP. Informed consent was obtained from patients in the study. At entry, basic clinical (age, comorbidity, symptoms and physical findings) and laboratory (white blood cell count) information commonly used by clinicians in the management of respiratory infections, was recorded. According to microbiological results, patients were assigned to the following categories: bacterial (*Streptococcus pneumoniae* and other pyogenic bacteria), virus-like (*Mycoplasma pneumoniae*, *Chlamydia* spp and virus) and unknown pneumonia. A scoring system to identify the aetiology was derived from the odds ratio (OR) assigned to independent variables, adjusted by a logistic regression model. The accuracy of the prediction rule was tested by using receiver operating characteristic curves.

One hundred and three consecutive patients were classified as having virus-like (48), bacterial (37) and unknown (18) pneumonia, respectively. Independent predictors related to bacterial pneumonia were an acute onset of symptoms (OR 31; 95% CI, 6–150), age greater than 65 or comorbidity (OR 6·9; 95% CI, 2–23), and leukocytosis or leukopenia (OR 2; 95% CI, 0·6–7). The sensitivity and specificity of the scoring system to identify patients with bacterial pneumonia were 89% and 94%, respectively. The prediction rule developed from these three variables classified the aetiology of pneumonia with a ROC curve area of 0·84.

Proper use of basic clinical and laboratory information is useful to identify the aetiology of CAP. The prediction rule may help clinicians to choose initial antibiotic therapy.

Key words: pneumonia; community-acquired; aetiology; prediction.

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Introduction

Community-acquired pneumonia (CAP) is one of the most common infectious diseases treated in ambulatory and hospital settings, and is associated with significant morbidity and mortality (1).

Traditionally, physicians have used information obtained from the history to select the initial antibiotic therapy in patients with CAP. However, previous studies have suggested that this information has a low sensitivity and specificity to predict the aetiology (2).

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We developed a prospective study with the aim of establishing the aetiology of CAP in our area. The microbial findings were then compared with information obtained from the history to determine whether the initial presentation can accurately predict the aetiology of CAP.

Methods

DATA COLLECTION

During a 15-month period from 1 January 1993 to 31 March 1994, demographic information and data on comorbidity, symptoms, signs, laboratory and chest radiographic findings were collected prospectively from consecutive patients 14 years of age or older admitted to the Emergency Department at the University Hospital

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Arnau de Vilanova, Lleida, Spain. To be included in the study, patients had to have a principal diagnosis of pneumonia according to the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) (3). We excluded patients who had been hospitalized within 7 days previous to the current admission or transferred from another acute care hospital. Clinical information was recorded on a standardized data form by the examining physician at the patient visit. Radiographic, laboratory and microbiological findings were recorded by investigators during follow-up.

MICROBIOLOGIC STUDIES

Two blood cultures were performed in all patients. Samples from lung parenchyma were also obtained by transthoracic needle aspiration (TNA) in patients without contraindications and after informed consent (4). In addition to conventional microbial testing, PCR tests to detect *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella penumophila* DNA were performed in TNA samples (5–8). Serologies on days 1 and 30 were performed to detect *Influenza* A virus, *Coxiella burnetii*, *Chlamydia psittaci* (complement fixation test), *L. pneumophila* (immunofluorescence test) and *C. pneumoniae* (microimmunofluorescence test) antibodies. If available, a sputum sample was stained and cultured.

Criteria for definitive microbial diagnosis were (i) blood, pleural or TNA culture yielding a pathogen; (ii) positivity of *S. pneumoniae* antigen detection test in TNA sample; (iii) positivity of PCR test for *S. pneumoniae*, *M. pneumoniae*, *C. pneumoniae* or *L. pneumoniae* in lung sample; (iv) a sputum culture yielding *L. pneumophila*; (v) a four-fold rise in antibody titers for *M. pneumoniae*, *C. pneumoniae*, *C. psittaci*, *L. pneumophila*, *C. burnetii* or *influenza* A virus, or a single IgG titre of >512 for *C. pneumoniae* antibodies.

CLASSIFICATIONS OF THE CATEGORY OF PNEUMONIA

According to microbial findings, patients were classified into the following categories of pneumonia (9):

1. Bacterial pneumonia **(BP)**: pneumonia caused by *S. pneumoniae* and other pyogenic bacteria (streptococci, *H. influenzae*, *Staphylococcus aureus* and *Enterobacteraceae*).
2. Virus-like pneumonia **(VP)**: pneumonia caused by *M. pneumoniae*, *C. pneumoniae*, *C. psittaci*, *C. burnetii*, *L. pneumophila* and virus.
3. Pneumonia of unknown aetiology: pneumonia in which all microbial work up provided negative results.

DATA PROCESSING AND SATISTICAL ANALYSIS FOR PREDICTION RULE

Patients with BP or VP were analysed. In step 1, basic information commonly used by clinicians in the management of respiratory infections and easy to obtain at bedside were first compared by univariate analysis in both groups. The following eight variables were analysed: age, co-morbidity, white blood cell count, and five variables related to initial clinical presentation [acute onset (less than a 24-period), chills, pleuritic chest pain, production of purulent sputum, and signs of consolidation at auscultation] (10). Candidate predictor variables were converted to dichotomous variables and classified into three categories: epidemiological (the presence or absence of age greater than 65 or co-morbidity), clinical (the presence or absence of the symptoms and signs above described), and biological (the presence or absence of an abnormal white blood cell count, defined as leukocytosis $\geq 11\times10^9 1^{-1}$ or leukopenia $\leq 4\times10^9 1^{-1}$). In step 2, only variables found to be statistically significant were included in a score system. According to the odds ratio assigned, adjusted by a logistic regression model, variables were scored in a scale from 0 to 5.

Comparison of variables among patients with different aetiologies was made by using chi-square with Yates' correction for continuity. All values of less than 0·05 were considered significatives. Sensitivity and specificity were calculated according to standard methods (11). Confidence intervals of 95% were used. The accuracy of the scoring model in discriminating the aetiology of pneumonia was evaluated by using the area under receiver operating characteristic (ROC) curve (12).

Results

PATIENT DEMOGRAPHICS

The final study population was constituted by 103 patients. The mean age was 51years (15–87). Forty-one (39·8%) were older than 65 years, and 35 (85·3%) come from their home. The male–female ratio was 1:38. Thirty-seven (35·9%) patients had co-morbidity (chronic bronchitis: 11; HIV infection: eight; chronic heart failure: seven; malignancy: four; chronic liver disease: three; diabetes: two; stroke: one; dementia: one). Respiratory failure ($PaO_2 < 60$ mm Hg) was present in 45 (43·6%) patients. Seventy-seven (74·7%) required hospitalization and three (4%) of them died.

AETIOLOGY OF PNEUMONIA

A definitive aetiological diagnosis was established in 85 (82·5%) patients. According to methods, patients were classified into having the following categories of pneumonia: (a) virus-like pneumonia: 48 (46·6%): *Chlamydia spp*: 21; Mycoplasma: 20; virus: five; *C. burnetii*; two; (b) bacterial pneumonia: 37 (35·9%): *S. pneumoniae*: 27; *H. influenzae*: seven; *Streptococcus viridans*: one; *Streptococcus pyogenes*; one; *Enterococcus faecium*: one; (c) Pneumonia of unknown aetiology: 18 (17·4%).

ANALYSIS OF DATA AND DEVELOPMENT OF THE SCORING SYSTEM

Comparison of basic epidemiological, clinical and biological variables between groups is shown in Table 1.

TABLE 1. Comparison of variables between categories of pneumonia and development of the scoring system

	Bacterial pneumonia $n=37$ %	Virus-like pneumonia $n=48$ (%)	*P*-value	OR* (95% CI)**	Score
Epidemiological					
Age >65 or co-morbidity	25 (68)	12 (25)	<0·05	6·9 (2–23)	3
Clinical					
Acute onset	28 (76)	10 (21)	<0·05	31 (6–150)	5
Chills	11 (31)	9 (19)	0·23	0·4 (0·1–1·6)	
Chest pain	25 (68)	23 (48)	0·07	0·8 (0·2–2·6)	
Purulent sputum	10 (27)	11 (23)	0·66	2·4 (0·6–9·1)	
Signs of consolidation	25 (68)	30 (63)	0·62	0·5 (0·1–2)	
Biological					
Leukocytosis or leukopenia	30 (81)	20 (41)	<0·05	2 (0·6–7)	2

*OR = odds ratio.**Cl = confidence interval.

Compared with VP patients, BP patients were more often older than 65 years of age or had a higher rate of comorbidity (68% *vs*. 25%; OR 6·9, 95% CI 2–23) and had abnormal white blood cell counts (81% *vs*. 42; OR 2, 95% CI 0·6–7). Among clinical variables only an acute onset of symptoms was statistically related to BP (76% *vs*. 21%; OR 31, 95% CI 6–150).

According to the level of the odds ratio assigned, independent variables were scored as follows: an acute onset of symptoms: five; an age greater than 65 years or comorbidity: three; leukocytosis or leukopenia: two (Table 1). After examining the clinicians priorities, several cut-off points were suggested: (a) when sensitivity in detecting BP patients was considered the end-point, a cut-off point of 5 was selected (sensitivity: 89%; specificity: 63%) (Table 2), and 85 (100%) patients could be classified; (b) when specificity of the scoring system was required, two cut-off points were selected: a score of 10 as specific point to identify BP patients (sensitivity: 57; specificity: 94%), and a score of 3 as a specific point to identify VP patients (sensitivity: 63%, specificity: 89%) (Table 2), and 58 (68%) patients could be classified. The area under the ROC curve was 0·84 (Fig. 1).

Discussion

The results of this study show that among patients with CAP, the aetiology of pneumonia could be discriminated on the basis of findings obtained from the history, physical examination and basic laboratory information. A prediction rule derived from data traditionally used by clinicians in the management of CAP such as age, comorbidity, the clinical presentation and white blood cell count, classified the aetiology of patients with a ROC curve area of 0·84, indicating good discrimatory power (13).

The specific aetiologic diagnosis in CAP patients is often delayed for several days until the results from sputum and blood cultures are available. Although Gram stain has been widely performed to provide rapid information on the aetiology of pneumonia there is limited evidence of its usefulness (14,15). In addition, serology is available for many respiratory pathogens, but it does not often provide diagnostic changes early enough to be clinically useful. In this situation, clinicians have tried to obtain information from the history to select the initial antibiotic therapy for the most likely pathogen.

This traditional practice has been questioned by the results of previous studies that have failed to find a relationship between clinical presentation and the pathogen responsible (16,17). The study by Farr *et al*. (16), provided a quantitative estimation of the difficulty on predicting the microbial aetiology on the basis of the presenting symptoms and signs at admission to hospital. They found that the four main categories of pneumonia (pneumococcal, mycoplasma, other and undetermined) could be predicted in only 42% of the patients. However, the use of unspecific microbial diagnostic criteria such as sputum culture and probably, a partial overlap of the categories, may explain the low discriminatory power of the prediction model. In other study, Fang *et al*. (17) did not find differences at presentation between pathogens causing pneumonia. However it must be said that 67% of patients included in the analysis has only a presumptive microbial diagnosis, and patients with pneumonia due to *M. pneumoniae* were inexplicably excluded.

In our study, we have tried to avoid the methodological limitations found in previous studies. First, only samples of undoubted specificity were analysed. Thus the sputum was changed for lung samples obtained by TNA, which has previously showed to have a high specificity in the study of lung infection (18–19). Second, the variables included in the study were carefully selected. Only basic clinical and biological information traditionally used in the management of respiratory infections and easy to obtain at bedside prior to antibiotic therapy being started, were included in

TABLE 2. Sensitivity and specificity of several cut-off points suggested

End-point	Score	Sensitivity % (95% CI*)	Specificity % (95% CI*)
Identification of patients with bacterial pneumonia	≥5	89 (78–96)	63 (54–81)
Identification of patients with bacterial pneumonia	10	57 (40–74)	94 (86–100)
Identification of patients with virus-like pneumonia	≤3	63 (48–77)	89 (78–100)

*CI = confidence interval.

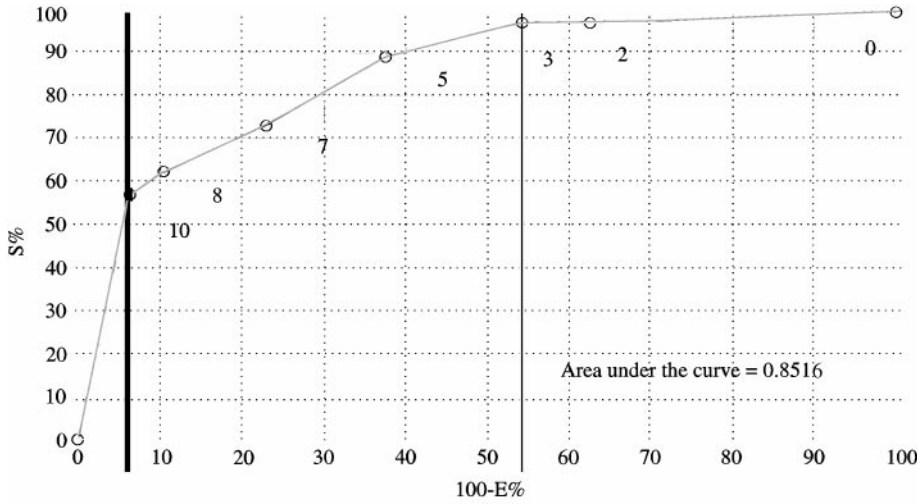

FIG. 1. Receiver-operating-characteristic curve for the combined score of the three epidemiological, clinical and laboratory variables. The zone to the left of the thick line indicates a high probability of bacterial pneumonia (score 10, specificity 94%). The zone to the right of the thin line indicates a high probability of virus-like pneumonia (score, <3, specificity 89%).

the prediction rule. Although radiographic findings have shown to be of some use in prediction of the aetiology of pneumonia (20), no attempt was made to include the chest radiograph in the analysis because problems in accesibility and interpretation to such a test (21). Third, a clinical usefulness of the prediction rule was a priority in the design of our analysis. It has been suggested that one of the main issues in the management of respiratory infections is to discriminate whether the pathogen belongs to either a bacterial a virus-like category in order to select either betalactamic or macrolide therapy, and our study contributes to solving this issue (9,22).

Previous studies have already found some distinct features between patients with CAP. Elderly and the presence of chronic conditions have been related to bacterial pathogens (23), and pneumonia due to Mycoplasma has been often diagnosed in young healthy populations (24). In addition, a higher rate of sputum production, pleuritic chest pain and leukocytosis have previously shown a tendency to be caused by *S. pneumoniae* (17,25). In a recent study (26), diarrhoea and increase creatine kinase was found to predict *L. pneumophila* pneumonia in the Emergency Department and proposes that, based on this information, clinicians should prescribe a macrolide antibiotic and apply rapid confirmatory tests. However, as recently suggested (27), there is little information in the literature of whether a constellation of variables can predict the aetiology of pneumonia. In a previous study (28), the presence of a combination of variables (cardiovascular chronic disease + an acute onset + pleuritic chest pain + leukocytosis + Gram-positive bacteria in the sputum Gram stain) identified 80% of infections due to *S. pneumoniae*. However, the need for microbiological study of respiratory sample makes this approach difficult to perform at bedside. Our score system was developed with the aim of selecting variables easy to

obtain by clinician and before empirical therapy was started.

The results of the present study may also help to solve this issue. The prediction rule based on the three main variables (epidemiological, clinical and biological) can be used as a sensitive or specific test depending on clinician's priorities. Thus, when a high specificity is required, two cut-off points are suggested: when a score of 10 is achieved (for example, age grater than 65 + an acute onset + leukocytosis), BP is the most likely aetiology (specificity 94%); when a score of 3 is achieved (for example, none of the variables are present), VP is the most likely aetiology (specificity 89%). Otherwise, when a high sensitivity is required, we suggest a score of 5 (for example, an acute onset, or age greater than 65 + leukocytosis). In this situation, the test identifies a high rate of patients with BP (sensitivity 89%).

We must address the potential limitations of our prediction rule before recommending its use in clinical practice. First, the analysis was performed in adults who presented to an Emergency Department for CAP therefore, some patients needed hospitalization (75%) and others were managed at home (25%). In our opinion, the prediction rule should be recommended to the same heterogeneous population. Thus, the introduction of the prediction rule in other populations would alter the power of discrimination. However, to have found differences between the aetiologies of pneumonia in such a heterogeneous sample would probably increase the model's robustness and generalizability to other clinical settings. The validation of this model in other samples could be solved this issue. Second, it has been suggested that concerns in predicting the aetiology in patients with CAP may arise from the fact that infections due to *Legionella* can have an overlap of features that includes both 'typical' and 'atypical' findings (2). This issue has not been solved in our study because we had no cases due to this microorganism. However, because CAP due to *Legionella* ranged widely depending on the geographic area studied (29), we suggest the incorporation of the prediction model in settings where *Legionella* infection is not currently considered. Finally, the score system developed from the study achieves good specificity rates at the expense of poor sensitivities. This means that certainty in identifying patients with bacterial pneumonia (score 10, specificity 94%) is achieved in only half of these cases (score 10, sensitivity 57%). Therefore, one should keep in mind that the score system may be useful in only a subset of patients.

In conclusion, among adults presenting with CAP, a prediction rule based on initial presentation accurately discriminated the aetiology of pneumonia. Recent guidelines (30) recommend the use of betalactam antibiotics as the therapy of choice in patients with lower tract respiratory infections and, in those with suspected infection due to atypical agents, macrolides should be then chosen. The incorporation of the prediction rule to clinical practice could help clinicians to choose or simplify (from biterapy to monoterapy) initial therapy in some cases. Further studies of validation in larger populations are needed.

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