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P. M. Olaechea
J. M. Quintana
M. S. Gallardo
J. Insausti
E. Maraví
B. Alvarez

A predictive model for the treatment approach to community-acquired pneumonia in patients needing ICU admission

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P.M. Olaechea (✉) · J.M. Quintana · M.S. Gallardo
Hospital de Galdakao, B° de Labeaga s/n, E-48960 Galdakao, Vizcaya, Spain
FAX: +34 (4) 456 6268

J. Insausti
Hospital de Navarra, Pamplona, Navarra, Spain

E. Maraví
Hospital Virgen del Camino, Pamplona, Navarra, Spain

B. Alvarez
Hospital General de Alicante, Alicante, Spain

Abstract *Objective:* To create a predictive model for the treatment approach to community-acquired pneumonia (CAP) in patients needing Intensive Care Unit (ICU) admission.
Design: Multicenter prospective study.
Setting: Twenty-six Spanish ICUs.
Patients: One hundred seven patients with CAP, all of them with accurate etiological diagnosis, divided in three groups according to their etiology in typical (bacterial pneumonia), *Legionella* and other atypical (*Mycoplasma*, *Chlamydia* spp. and virus). For the multivariate analysis we grouped *Legionella* and other atypical etiologies in the same category.
Methods: We recorded 34 variables including clinical characteristics, risk factors and radiographic pattern. We used a multivariate logistic regression analysis to find out a predictive model.
Results: We have the complete data in 70 patients. Four variables: APACHE II, (categorized as a dummy variable) serum sodium and phosphorus and "length of symptoms" gave an accurate predictive model ($c = 0.856$). From the model we created a score that predicts typical pneumonia with a sensitivity of 90.2% and specificity 72.4%.
Conclusion: Our model is an attempt to help in the treatment approach to CAP in ICU patients based on a predictive model of basic clinical and laboratory information. Further studies, including larger numbers of patients, should validate and investigate the utility of this model in different clinical settings.

Key words Community-acquired infections · Bacterial pneumonia · Intensive Care Units · Logistic models

Introduction

Establishing an etiological diagnosis of community-acquired pneumonia (CAP) in patients admitted to Intensive Care Units (ICU) is still controversial. Causal micro-organisms are only known in 50–72% of the cases [1–8]. Therefore, the therapy should frequently be based upon empirical regimens with a broad spectrum of coverage against both bacterial and non-bacterial agents. Community-acquired pneumonia has been classified, depending on its clinical features, into typical and atypical. The first group includes pneumonia caused by *Streptococcus pneumoniae* and other aerobic bacteria. The second group includes *Legionella* spp., *Mycoplasma pneumoniae*, *Chlamydia* spp., and viruses. This classification has been questioned lately [9, 10].

In some cases, *Legionella* spp. was considered as clinically atypical [11–13], typical in others [2, 14, 15] or not included in any group [16]. Clinical parameters were shown to have low value in predicting the etiology of CAP [17–21]. However, some studies [7, 16, 20, 21] found significant differences in the univariate analyses of these parameters. Recently, some authors [19, 20] attempted to estimate the etiological diagnoses by reviewing the medical histories, and the findings of physical examination.

The aim of the present study is 1) to compare the clinical and radiologic characteristics of typical, *Legionella* group, and other atypical CAP, and 2) to develop a predictive model, by multivariate analysis, capable of guiding the treatment of a pneumonia episode.

Materials and methods

From November 1st, 1991 to October 31st, 1992, we prospectively studied 262 consecutive patients with community-acquired pneumonia (CAP) who were admitted to one of the 26 Intensive Care Units in Spain belonging to the "ICU Community-Acquired Pneumonia Study Group."

For the purpose of the study, suspicion of pneumonia was based upon the presence of at least one of the following "major criteria": cough, sputum production or fever higher than 37.8 °C, or two of the following "minor criteria": pleuritic chest pain, dyspnea, altered mental status, pulmonary consolidation on examination and white blood cell count higher than 12 000 mm^3 [16]. Clinical suspicion was confirmed by the presence of chest radiographic infiltrates with/without pleural effusion. Patients in whom chest roentgenogram abnormalities were attributed to other causes were excluded. Only those pneumonias with definite microbial etiology and specific clinical features were considered for the present study.

One of the following criteria was used to consider the microbiological diagnosis as definite: a) quantitative cultures of protected specimen brush or bronchoalveolar lavage yielding 10^3 or more and 10^4 or more CFU/ml, respectively; b) positive blood cultures for the same micro-organism as that isolated from respiratory secretions; c) positive pleural fluid cultures; d) isolation of *Pneumocystis carinii* or positive culture of *Legionella* spp. or *Mycobacterium tuberculosis* obtained from respiratory secretions; e) a 4-fold or more rise in antibody titres for *Legionella*, *Mycoplasma pneumoniae*, *Chlamydia* spp., *Coxiella burnetti* and viruses. Probable etiology was defined as the positive culture of a pathogen from respiratory secretions without any other culture available, and unknown etiology when no pathogen was isolated. A total of 107 out of 262 (41%) patients who were initially enrolled met the above mentioned criteria and were enrolled in the study. Other patients were excluded from the study: 108 cases with CAP of unknown etiology or incomplete data, 31 with probable etiology of their CAP, 12 pneumonias caused by *Pneumocystis carinii* and *Mycobacterium tuberculosis*.

For the univariate analysis, patients were classified according to the microbiological etiology as follows: a) typical CAP: patients with definite bacterial CAP (except *Legionella* spp.); b) *Legionella* group, and c) other atypical CAP, patients with CAP caused by viruses, *Mycoplasma*, and *Chlamydia* spp. The following data were recorded from each patient: Acute Physiology and Chronic Health Evaluation Score (APACHE II) on admission [22], age, gender, duration between appearance of symptoms and ICU admission (days). The recorded clinical variables were: fever 38 °C or more, purulent sputum production and pleuritic chest pain.

For the analysis of risk factors for increased mortality or morbidities, 21 variables were recorded from each patient, as described elsewhere [23, 24]. These included underlying diseases as well as toxic habits. Underlying diseases were classified, according to McCabe et al. [25], into 1) non-lethal, chronic or potentially curable; 2) lethal in a medium duration (death predicted within 4–5 years); and, 3) rapidly lethal; no patients belonged to this last group.

The following hematological and laboratory values were recorded: cellular blood count, serum sodium, phosphorus, total proteins, albumin, and creatinine. Hyponatremia was defined as sodium levels below 130 mEq/l; hypophosphatemia as serum phosphorus levels below 2.5 mg/dl. Chest X-rays were performed in the ICU with the patient in the supine position. The presence of alveolar or interstitial condensation as well as pleural effusion was assessed. Radiographic patterns were classified into three groups: alveolar, interstitial, and mixed.

The results are expressed as the mean ± SD for quantitative variables. Discrete data are expressed in the tables as the percentages of patients from each group presenting the factor. For the univariate analysis the chi-square test, and the two-tailed *t*-test were performed. Also, non-parametric tests were employed where appropriate (Wilcoxon, Kruskal-Wallis). Generalized linear models were used to compare the three etiological groups. For multiple comparison, Scheffé's test was performed.

We took the following criteria to select the variables for the multivariate model: a) $p < 0.05$ in the univariate analysis either in the table with typical, *Legionella* and other atypical etiologies or when having *Legionella* and another atypical etiology in a single atypical group. b) Additionally, univariate results for each variable in the *Legionella* and other atypical group should be similar to allow us put them together in a single final atypical group. Of all the possible combinations, we chose the one with higher "*c*" scores and better clinical application. Dummy variables were used for APACHE II scores that were categorized into three groups (≤ 15, >15 to ≤ 20, and >20, indicating mild, moderate, and severe degree of severity, respectively). The duration of symptoms was included as a continuous variable.

In the multivariate analysis the *Legionella* group was included in the atypical CAP category. The predictive model was applied to 70 out of 107 patients. In 32 patients phosphorus was not recorded, since this is not a routine procedure in some emergency rooms. In six patients, the duration of symptoms could not be determined precisely.

A score was computed out of this model, assigning the β coefficient of the chosen variables. The cut-off point that offered the best equilibrium between sensitivity and specificity was determined. The strength of the model was evaluated by means of a receiver operator characteristic (ROC) curve. All *p* values less than 0.05 were considered statistically significant. All data were introduced in a data base and analyzed using the SAS statistical package.

Results

Table 1 shows the causal micro-organism in the 69 patients with typical CAP, and the 38 with atypical CAP. Patients with typical CAP or *Legionella* had higher APACHE II scores as compared to those with CAP caused by other etiologies (21.6, 19.1 and 12.9 mean APACHE II scores for the three groups, respectively, $p = 0.001$). Also, patients of the last group were younger than the other two, although statistical significance was only shown when compared to those with

Table 1 CAP: etiological diagnosis in the complete group ($n = 262$)

Etiology	n (%)
– Unknown etiology	108 (41.2)
– Known etiology	107 (40.8)
Typical pneumonia	69 (26.3)
Streptococcus pneumoniae	30
Haemophilus influenzae	10
Staphylococcus aureus	10
Escherichia Coli	3
Pseudomonas aeruginosa	3
Klebsiella pneumoniae	2
Other streptococci	4
Other bacteria and polymicrobial etiology	7
Atypical pneumonia	38 (14.5)
Legionella pneumophila	21
Mycoplasma pneumoniae	8
Virus	5
Chlamydia psittaci	4
– Probable diagnosis	31 (11.8)
– Pneumocystis carinii and mycobacteria	12 (4.6)
– Mixed (typical-atypical)	4 (1.5)

typical CAP (40.5 versus 55.2 years: $p = 0.001$) (Table 2). There were no statistical differences regarding the frequency of fever and chest pain, however purulent sputum was less frequent in patients with CAP caused by atypical germs other than *Legionella* ($p = 0.05$). The mean duration of symptoms before ICU admission was shorter in the typical CAP group as compared to both the other groups (4.8 versus 6.8 and 6.9 days; $p = 0.096$).

Among the risk factors we studied, only the underlying disease as described by McCabe [25] showed statistically significant differences between fatal outcome in patients with typical CAP (30%), as compared to none in the *Legionella* group and 6.7% in the atypical CAP group ($p = 0.011$).

Table 3 illustrates the main results of blood analysis, biochemistry and radiologic features. Sodium and phosphorus levels were higher in the typical CAP group compared to both other groups (137 versus 130 mEq/l for sodium; $p < 0.001$, and 3.3 versus 2.2 mg/dl for the phosphorus; $p = 0.009$, for the *Legionella* groups, respectively). Serum creatinine levels were similar in patients with typical CAP and *Legionella* infection (1.7 mg/dl), but higher than that of the atypical CAP group (0.9 mg/dl)($p = 0.019$). Overall, the radiographic pattern differed from one group to another ($\chi^2 = 22.8$; $p = 0.001$). Patients with typical CAP and *Legionella* had more frequent alveolar patterns on their chest radiographs (84.6% and 90.5%), while patients from the atypical CAP group had a similar distribution between alveolar and interstitial patterns (41.2%). (Table 3). The extension of radiographic infiltrates (one lobe, one lung, or both lungs) was not different among the three groups. Pleural effusion was relatively common among patients with typical CAP and CAP caused by *Legionella* (25.8 and 23.8%); while this was rare in the remaining group of patients (5.8%; p = NS).

To create the best predictive model, we performed a logistic regression analysis including patients with *Legionella* in the same group of atypical CAP; thereby yielding two groups: typical and atypical CAP. The discriminating variables between these two groups were: APACHE II score (considered as a categoric and dummy variable), serum sodium, serum phosphorus and duration of symptoms of the disease in days. Table 4 shows the β coefficients and the 95% confidence intervals of the final logistic regression model, out of which a score was derived (shown in Table 5). The area below the curve (ROC) was $c = 0.856$. The score was determined by adding the values for each factor, but substracting the duration of symptoms (multiplying the number of days by 0.15). Using a cut-off point of 3 or more, the model predicted the presence of typical CAP with a sensitivity of 90.2% and a specificity of 72.4%. The positive predictive value was 84%, and the negative predictive value 82%.

Table 2 Patients' general and clinical characteristics by pneumonia etiological group

Clinical data	Typical $n = 69$	Legionella $n = 21$	Other atypical $n = 17$	p
APACHE II	21.6 ± 7.7*[a]	19.1 ± 7.5*[a]	12.9 ± 5.3*[b]	0.001
Age (years)	55.2 ± 18.3*	52.9 ± 9.6	40.5 ± 18.7*	0.001
Gender (male)	69.6%	80.9%	64.7%	NS
Duration of symptoms (days)	4.8 ± 3.8	6.8 ± 5.6	6.9 ± 4.8	NS
Fever (≥ 38.5 °C)	82.4%	90.5%	100%	NS
Purulent sputum	59.1%	66.7%	29.5%	0.05
Chest pain	56.1%	47.6%	52.9%	NS

* Multiple comparisons Scheffé's test $p < 0.05$
[a] No differences between [a] groups
[a – b] Statistically signicant results (Scheffé's test)

Table 3 Main results of blood analysis, blood chemistry, and chest radiograph

Variable	Typical $n = 69$	Legionella $n = 21$	Other atypical $n = 17$	p
Blood analysis ($\times 10^9$/l)[a]				
Leukocytes	15.8 ± 15.0	12.9 ± 11.2	12.1 ± 7.8	N.S.
Neutrophils	13.0 ± 10.8	11.3 ± 9.5	10.0 ± 7.2	N.S.
Lymphocytes	1.2 ± 1.1	0.9 ± 0.9	1.8 ± 3.2	N.S.
Platelet	215 ± 118	151 ± 93	213 ± 130	N.S.
Biochemistry [a]				
Sodium (mEq/l)	136.8 ± 8.0*	129.8 ± 5.9*	133.3 ± 6.4	0.001
Phosphorus (mg/dl)[b]	3.3 ± 1.5*	2.2 ± 0.8*	2.6 ± 1.0	0.009
Proteins (gr/dl)[c]	5.4 ± 0.8	5.2 ± 0.5	5.7 ± 0.5	N.S.
Albumin (gr/dl)[c]	2.7 ± 0.5	2.6 ± 0.4	2.9 ± 0.7	N.S.
Creatinine (mg/dl)	1.7 ± 1.1*	1.7 ± 1.5	0.9 ± 0.2*	0.019
Chest radiograph				
Radiographic pattern [d]				0.001
Alveolar	84.6%	90.5%	41.2%	
Interstitial	4.6%	4.7%	41.2%	
Mixed	10.7%	4.7%	17.6%	
Localization				N.S.
One lobe	31.8%	20.0%	25.0%	
One lung	30.3%	35.0%	0.0%	
Bilateral	37.8%	45.0%	75.0%	
Pleural effusion	25.8%	23.8%	5.8%	N.S.

[a] mean ± sd
[b] typical $n = 45$; Legionella = 17; other atypical $n = 13$
[c] typical $n = 55$; Legionella = 21; other atypical $n = 17$
[d] typical $n = 65$; Legionella = 21; other atypical $n = 17$
*Multiple comparisons Scheffé's test $p < 0.05$

Table 4 Predictive model by multivariate logistic regression analysis

Variable	β coefficient	95% Confidence interval
APACHE II		
(≤15)	1	–
(>15 to ≤20)	1.287	−0.316–2.891
(>20)	2.053	0.542–3.564
Sodium ≥ 130 mEq/l	2.321	0.747–3.896
Phosphorus ≥2.5 mg/dl	2.266	0.821–3.711
Duration of symptoms (days)	−0.147	−0.283– −0.01

$c = 0.856$

Table 5 Score constructed applying the predictive model

Variable	Score
APACHE II	
≤ 15	0
> 15 to ≤ 20	1
> 20	2
Sodium < 130	0
≥ 130	2.5
Phosphorus < 2.5	0
≥ 2.5	2.5
Duration of symptoms (days)	−0.15 × day

Discussion

In our study, we found that patients with atypical pneumonia are younger and have a lower APACHE II at admission. The percentage of patients with purulent sputum was also lower than in the other categories. Among laboratory results, serum sodium and phosphorus levels were lower in the *Legionella* group, while creatinine was lower in the atypical group. Typical and *Legionella* groups present an alveolar X-ray pattern, more frequently, but this was similar in the two groups. Interstitial pattern was more prevalent in the atypical group.

Our purpose was to find a practical model to help in the treatment approach of CAP patients at the time of admission. In the multivariate analysis we found that APACHE II score, serum sodium and phosphorus and the duration of symptoms previous to admission on the ICU, were independent factors with a predictive value for discriminating both typical and atypical pneumonia groups. We established a scoring system (Table 5). The cut-off point to distinguish both groups was 3 points or more. The sensitivity and specificity using this score was 90.2% and 72.4%, respectively, to predict a typical pneumonia. This was

Table 6 Sensitivity and specificity of the predictive model vs microbiological diagnosis

		Microbiological diagnosis		
	Score	Typical	Atypical	Total
Predictive Score	≥ 3 (Typical)	37	8	45
	< 3 (Atypical)	4	21	25
Total		41	29	70

Sensitivity: 90.2%; Specificity: 72.4%

associated with a 17.7% false-positive rate, and only a 9.7% false-negative rate.

Clinical, radiographic, and epidemiological criteria are commonly used to guide empirical antibiotic treatment and further microbiological studies in patients with community-acquired pneumonia (CAP) admitted to an ICU. In a previous study from our group, only 61% of the patients with CAP were empirically treated with antibiotic combinations that allowed broad-spectrum coverage for both typical and atypical agents. Thirty-six percent received antibiotics with inadequate coverage of atypical micro-organisms, while 3% received erythromycin alone as empirical treatment. In other studies [3, 5, 23] patients were treated with antibiotic combinations that partially cover both types of micro-organisms, probably based on epidemiological data. Spanish authors [2, 26] describing series with a high percentage of *Legionella*, suggested that initial antibiotic regimens should include erythromycin.

These data confirm that physicians are aware of the clinical and epidemiological aspects related to that kind of patient, regarding the initiation of antibiotic treatment, although this issue has not been statistically validated yet. The Guidelines of the American Thoracic Society [19], make reference to the excessive overlapping of signs and symptoms of CAP with other infectious and non-infectious processes. Other studies [18, 24, 26–30] confirm this finding. Nevertheless, univariate analyses show marked differences among the groups; a fact that does not allow the individual prediction of the etiology of pneumonia.

Our patients have been admitted to one of the many participating ICUs, which implies a considerable severity of the pneumonia episode. In other words, this could be manifested in clinical and laboratory parameters, thus explaining the differences from other studies. However, our data might not be valid for patients with lower degrees of severity. Our study design was to select a group of patients with accurate etiological diagnosis. For that reason, the criteria for establishing the diagnosis were very strict, hence reducing the number of patients included. The inability to establish an etiological diagnosis was the cause of the exclusion of 53.7% of the patients. For the multivariate analysis, only 70 patients were included who had all their data recorded. Missing values were frequent (e.g., serum phosphorus could not be determined in 32 patients in the emergency room). Although this could be considered as a drawback when determining management by using our score, yet it leads the way for future studies. Before we can confidentially suggest the use of this score, another group or larger series should be tested in order to reach definite conclusions.

Another limitation of our study is the allocation of patients to one or another group. For instance, including all patients with typical microbial etiology (except *Legionella*) might be questionable from the microbiological point of view, yet we considered it as a highly functional aspect, since no differences have been reported as regards etiologies [7]. By the same token, we gathered into the same group patients with CAP caused by *Legionella* spp., *Mycoplasma pneumoniae*, *Chlamydia* spp., and viruses. The reason was that the clinical pictures were similar, although not overlapping, and that the initial treatment is basically the same, except for viruses.

Our study shows that Legionella CAP patients present higher degrees of severity, the presence of purulent sputum and alveolar X-ray patterns and they are older than atypical CAP patients. From these points, they would be closer to the clinical definition of typical CAP. Nevertheless, duration of symptoms and the levels of serum sodium and phosphorus are closer to atypical CAP. It can be argued whether the category 'atypical' refers to a particular clinical presentation [31], or to a group of etiological agents (so called "atypical") with roughly similar clinical presentation but the same treatment, generally macrolides [32]. Only viral atypical CAP would be excluded from that treatment approach. Their inclusion in the 'atypical' group is based on clinical similarities. That is why the initial treatment approach to these patients is similar to other atypical cases.

Hyponatremia and hypophosphatemia were described as characteristics in initial studies concerning *Legionella* spp. [27–30]. In our study, these two variables were found to be risk factors in the univariate analysis. Granados and colleagues [17] found that hyponatremia was more frequent, although not statistically significant, in patients with pneumonia caused by *Legionella* spp. (17%) compared to those with *Streptococcus pneumoniae* (3%). Hyponatremia has been reported to be a poor prognosis factor in some series [23]. Leukocytosis has been shown to be a feature of pneumococcal pneumonia by some authors [21, 33, 34]. In our study we did not find this to be a distinguishing factor.

In summary, using a logistic regression model, the APACHE II score on admission, serum sodium, serum

phosphorus and the duration of symptoms of the disease were found to be independent factors differentiating between the two groups. Based on these findings, we produced a scoring system that could guide the initial management of these patients. We think that the present trends should not be modified until this predictive model is widely validated. The present study warrants further investigation in this field.

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Appendix

Members of the Grupo Español de Estudio de Neumonia Comunitaria en UCI: J. Rello (Hospital Clínico de Barcelona, Barcelona), J. Serra (Hospital General Vall D'Hebron, Barcelona), M.A. León Regidor (Hospital General de Cataluña, Barcelona), F. Alvarez Lerma (Hospital del Mar, Barcelona), I. Cherta (Hospital de Bellvitge, Barcelona), F. Barcenilla (Hospital Arnau de Villanova, Lerida), M. Chánovas (Hospital Virgen de la Cinta, Tortosa, Tarragona), R. Jordá (Hospital Son Dureta, Palma de Mallorca), M.J. Lopez Pueyo (Hospital General Yagüe, Burgos), M.J. Lopez Cambra (Hospital General de Segovia, Segovia), B. Oteo de la Vara (Hospital Clinico San Carlos, Madrid), V. Gonzalez (Hospital Miguel Servet, Zaragoza), E. Maravi (Hospital Virgen del Camino, Pamplona, Navarra), J. Insausti (Hospital de Navarra, Pamplona, Navarra), P. Olaechea and M.S. Gallardo (Hospital de Galdakao, Galdakao, Vizcaya), M.D. Sandar (Hospital Juan Canalejo, La Coruña), A. Martinez Pellús (Hospital Virgen de la Arrixaca, Murcia), F. Felices (Hospital Universitario, Murcia), J.A. Melgarejo (Hospital Santa Maria del Rosell, Cartagena, Murcia), P. Ibañez (Hospital Lluis Alcañiz, Xativa, Valencia), B. Alvarez Sanchez (Hospital General de Alicante, Alicante), J. Gudín (Hospital La Fe, Valencia), C. León Gil (Hospital N^a Sra. de Valme, Sevilla), A. Sanz (Hospital General Basico, Motril, Granada), E. Perez Ortiz (Residencia Sanitaria de Torrecárdenas, Almeria) and J.M. Aguado (Hospital de Merida, Merida, Badajoz).

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