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# Prognosis in Patients With Pneumonia and Chronic Obstructive Pulmonary Disease

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**OBJECTIVE: To study the incidence, severity, and mortality rates of pneumonia in a cohort of chronic obstructive pulmonary disease (COPD) patients monitored over 3 years.**

**PATIENTS AND METHODS: A total of 596 patients diagnosed with COPD according to spirometric criteria were included in the study. The variables assessed were mortality and severity according to the Pneumonia Severity Index (PSI) for community-acquired pneumonia (CAP).**

**RESULTS: Of the 596 patients included in the study, 75 (12.6%) developed at least 1 episode of pneumonia during the 3 years of the study. The overall incidence of pneumonia was 55.1 per 1000 person-years. There were 88 episodes in 75 patients. COPD severity, evaluated based on percentage of predicted $FEV_1$, was mild in 9 patients, moderate in 24, and severe in 42. Seventy-six (86.3%) episodes were CAP and 12 (13.6%) were acquired in hospital. Fourteen CAP cases corresponded to PSI group V, 28 to group IV, 20 to group III, and 14 to groups I and II. Overall mortality was 12.5% (11/88). The mortality rate was 41.7% (5/12) for nosocomial cases and 7.8% (6/76) for CAP cases (OR, 6.67; 95% confidence interval, 1.65-26.93). Assessing CAP mortality by level of severity, we found that the mortality rate was 35.7% (5/14) for group V and 3.5% (1/28) for group IV. No deaths occurred among patients in the other severity groups.**

**CONCLUSIONS: The incidence of pneumonia in COPD patients is high. More than half the cases of CAP (55.2%) in our COPD patients were classified in PSI risk groups IV and V.**

**Key words:** *Chronic obstructive pulmonary disease (COPD). Pneumonia. Mortality. Epidemiology. Incidence.*

## Evaluación pronóstica de las neumonías en pacientes con EPOC

**OBJETIVO: Estudiar la incidencia, gravedad y mortalidad de las neumonías ocurridas en una cohorte de pacientes con enfermedad pulmonar obstructiva crónica (EPOC) seguidos durante 3 años.**

**PACIENTES Y MÉTODOS: Se incluyó en el estudio a 596 pacientes con diagnóstico espirométrico de EPOC. Los parámetros a evaluar fueron la mortalidad y la gravedad valorada de acuerdo con el Pneumonia Severity Index (PSI) para la neumonía adquirida en la comunidad (NAC).**

**RESULTADOS: De 596 pacientes incluidos en el estudio, 75 (12,6%) desarrollaron al menos un episodio de neumonía durante el seguimiento. La incidencia global de neumonía fue de 55,1 por 1.000 personas-año. Hubo 88 episodios en 75 pacientes. El grado de la EPOC, valorado según el $FEV_1$ como porcentaje del teórico, era en 9 pacientes leve, en 24 moderado y en 42 grave. De los episodios de neumonía, 76 (86,3%) fueron adquiridos en la comunidad y 12 (13,6%) en el hospital. Al valorar la gravedad de la NAC, 14 episodios correspondían al grupo V, 28 al grupo IV, 20 al grupo III y 14 a los grupos I y II. La mortalidad global fue del 12,5% (11/88). La mortalidad en las neumonías nosocomiales fue del 41,7% (5/12) y la mortalidad en las NAC fue del 7,8% (6/76) (OR: 6,67; intervalo de confianza del 95%, 1,65-26,93). Al valorar la mortalidad en las NAC según la gravedad, se encontró que la mortalidad en el grupo V fue de un 35,7% (5/14), en el grupo IV del 3,5% (1/28) y nula en el resto de los grupos.**

**CONCLUSIONES: Hay una elevada incidencia de neumonía en los pacientes con EPOC. Más de la mitad de las NAC (55,2%) ocurridas en nuestros pacientes con EPOC están dentro de los grupos de riesgo del PSI IV y V.**

**Palabras clave:** *Enfermedad pulmonar obstructiva crónica (EPOC). Neumonía. Mortalidad. Epidemiología. Incidencia.*

## Introduction

Community-acquired pneumonia (CAP) is a common disease with a big impact on health services due to the burden it imposes on health resources.[1,2] According to the British guidelines based on prospective studies of the populations of the United Kingdom, Finland, and

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North America, the annual incidence of CAP is between 5 and 11 cases per 1000 persons among adults.[3] The incidence varies with age, being 20 per 1000 per year in persons over 60 and 34 per 1000 in persons over 75.

In 1997, Fine et al[4] developed a system that stratified CAP severity according to the risk of death. The system, which included demographic data, comorbidity, and physical, analytical, and radiographic findings, was subsequently validated with more than 50 000 patients,[5] and came to be called the Pneumonia Severity Index (PSI). The absence of chronic obstructive pulmonary disease (COPD) among the diseases associated with a high mortality risk was a surprising result given that COPD is known to increase the risk of pneumonia and that patients with COPD frequently have respiratory infections.[6]

Inpatient mortality from CAP ranges from 5% to 14%.[7,8] When patients require intensive care, mortality from CAP rises to 50%.[9] COPD affects 9% of the Spanish population between 40 and 70 years of age[10] and causes high rates of morbidity and mortality.[11] COPD comorbidity in CAP patients may well increase mortality and this increase would be related to the severity of bronchial obstruction or the presence of chronic respiratory insufficiency.[12]

The objective of this study was to determine the overall incidence of pneumonia (CAP and nosocomial) in COPD patients, to describe the severity of the pneumonia using current systems of assessment, to quantify the mortality of pneumonia in COPD patients, and assess the influence of COPD comorbidity.

## Patients and Methods

This was a retrospective cohort study of 596 patients diagnosed with COPD. Data were collected for the period October 1999 until July 2004 to allows each case to be followed up for 3 years. The mean period of follow-up of patients (taking into consideration deaths during the study period) was 979 days (range, 20-1454). All cases came from a controlled, randomized, clinical trial on the effectiveness of antipneumococcic vaccinations and had been consecutively enrolled from the outpatients clinic of our department (both inside and outside the hospital) and from the pneumology and internal medicine hospital wards. Enrollment criteria included age of more than 18 years, no prior antipneumococcic vaccinations, and a COPD diagnosis based on clinical and spirometric findings. The following exclusion criteria were established: pregnancy and immunocompromise (defined by the presence of known neoplasm, renal insufficiency in dialysis, human immunodeficiency virus infection, hypogammaglobulinemia, or anatomic or functional asplenia). Patients were classified according to their degree of bronchial obstruction—measure by the forced expiratory volume in 1 second ($FEV_1$) expressed as a percentage of the predicted value—following the recommendations of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).[13]

Diagnosis of pneumonia was made according to the British guidelines[3] and a chest x-ray was performed on all patients. The following data was collected from all patients with pneumonia: demographic data including age and sex, the items on the Fine scale (detailed below), and additional items such as other associated comorbidities (diabetes, alcoholism, active smoking addiction, corticosteroid use, pneumonia during the previous 3 years, and immunosuppressant therapy), presence of leukocytosis or leukopenia, radiographic findings (cavitation, bilateral, or multilobular involvement), microbiological data, and information on the progression of the pneumonia, need for intensive care or mechanical ventilation (invasive or not) and, in case of death, the main cause and whether it was related or not to the pneumonia. The Fine scale criteria included neoplastic disease, defined as any cancer except skin cancer that was present when pneumonia was diagnosed or in the first year following the pneumonia; liver disease defined as any clinical or histologic diagnosis of cirrhosis or other chronic liver disease such as active chronic hepatitis; heart disease, defined as systolic or diastolic ventricular dysfunction documented in the medical history or by physical examination, chest x-ray, echocardiography, scintigraphy, or ventriculography of the left ventricle; cerebrovascular disease, defined as clinical diagnosis of cerebrovascular accidents or transitory ischemic attacks documented by nuclear magnetic resonance or computed tomography; and kidney disease, defined as a history of chronic kidney disease, without including patients on dialysis which was an exclusion criteria. The protocol was also completed in cases of nosocomial pneumonia without applying a severity scale.

### *Statistical Analysis*

Analysis was performed using the statistical program SPSS for Windows, version 12. Qualitative variables were compared using the $\chi^2$ or Fisher tests and quantitative variables were compared with the Wilcoxon test. A multivariate logistic regression analysis was subsequently performed in which the dependent variable was the development of pneumonia (yes/no) and the independent variables were the ones found to be significant in the univariate analysis. The degree of bronchial obstruction was assessed using the $FEV_1$ (% of predicted), dichotomized as less than and equal to or greater than 40%.

## Results

During the study, 88 episodes of pneumonia were recorded (12 of them nosocomial) in 75 patients—73 men and 2 women. Of these, 64 patients presented a single episode, 9 patients presented 2 episodes, and 2 patients 3 episodes. The distribution of pneumonia

TABLE 1
**Incidence of Community-Acquired Pneumonia per 1000 COPD Cases per Year***

| | CAP | Persons per Year | Rate (per 1000 COPD/Year) |
|---|---|---|---|
| Total | 76 | 1597.3 | 47.6 |
| <65 years | 23 | 569.3 | 40.4 |
| ≥65 years | 53 | 1026.9 | 51.6 |
| $FEV_1$, <40% of pred | 41 | 644.5 | 63.6 |
| $FEV_1$, ≥40% of pred | 35 | 952.0 | 36.8 |

*COPD indicates chronic obstructive pulmonary disease; CAP, community-acquired pneumonia; $FEV_1$, forced expiratory volume in 1 second; pred, predicted.

TABLE 2
**Characteristics and Functional Test Results of COPD Patients With and Without Pneumonia**

| | With Pneumonia (n=75) | Without Pneumonia (n=521) | *P*† |
|---|---|---|---|
| Age, years* | 70.0 (63.4-76.4) | 67.9 (61.2-73.2) | .020 |
| Sex, male/female | 73/2 | 492/29 | .226 |
| BMI* | 27.1 (23.5-30.5) | 29.1 (25.8-32.7) | .003 |
| FVC (L)* | 2.0 (1.6-2.5) | 2.1 (1.6-2.6) | .310 |
| FVC%* | 59 (47-73) | 63 (51-74) | .245 |
| $FEV_1$, L* | 0.9 (0.7-1.3) | 1.1 (0.8-1.4) | .011 |
| $FEV_1$, % pred* | 38 (29-51) | 43 (33-55) | .043 |
| $FEV_1$/FVC%* | 51 (44-60) | 55 (45-64) | .034 |
| PPV23 | 38 (50.7%) | 260 (49.9%) | 1.000 |
| Current smoker | 14 (18.7%) | 128 (24.6%) | .329 |
| Neoplastic disease | 6 (8%) | 28 (5.4%) | .515 |
| Liver disease | 1 (1.3%) | 1 (0.2%) | .596 |
| CHF | 29 (38.7%) | 133 (25.5%) | .024 |
| Cerebrovascular disease | 3 (4%) | 7 (1.3%) | .2331 |

*Data expressed as median (interquartile range 25-75).
COPD indicates chronic obstructive pulmonary disease; BMI, body mass index; FVC, forced vital capacity; $FEV_1$, forced expiratory volume in 1 second; pred, predicted; $FEV_1$/FVC%, the ratio expressed as a percentage; PPV23, 23-valent polysaccharide pneumococcal vaccine; CHF, congestive heart failure.
†Results obtained using the Fisher test or the Wilcoxon test.

patients in function of the severity of COPD assessed by $FEV_1$ was the following: 9 patients were classified as mild (12%), 24 moderate (32%), and 42 severe (56%).

The overall incidence of pneumonia (CAP and nosocomial) was 55.1 per 1000 COPD patients per year. The CAP incidence in COPD patients is shown in Table 1 by age groups and severity of bronchial obstruction.

Demographic characteristics and lung function findings are shown in Table 2. Patients with pneumonia were significantly older, had a lower body mass index, and greater airflow limitation (lower $FEV_1$ expressed in liters and as percentage of the predicted value, and a lower ratio of $FEV_1$ to forced vital capacity expressed as a percentage).

Comorbidity analyzed in accordance with Fine criteria and exclusion criteria (only immunocompetent patients were included) revealed significant differences only for heart disease and pneumonia patients; the other variables were not significant. The multivariate analysis, presented in Table 3, shows the influence of each of the significant variables found in the univariate analysis.

Of the 88 pneumonia episodes, 73 (83%) were treated in hospital and 15 in outpatient clinics. An etiological diagnosis was obtained in 23 cases (26%): 14 episodes were caused by gram-negative bacilli, 2 by fungi (*Aspergillus* and *Nocardia* species), 2 by *Staphylococcus aureus,* 5 by pneumococci, and the 65 remaining episodes were of unknown etiology. There were 12 nosocomial pneumonias, which were not included in the severity analysis: 8 were known to be nonpneumococcal and 4 were of unknown etiology. There were 6 cases of polymicrobic etiology. None of the pneumococcal cases were in vaccinated patients.

Analyzing the distribution of CAP patients by PSI risk groups revealed that 18.4% (14/76) corresponded to groups I and II, 26.3% (20/76) to group III, 36.8% (28/76) to group IV, and the remaining 18.4% (14/76) to group V. Four of the 14 pneumonia patients from groups I and II, 16 of the 20 from group III, 27 of the 28 from group IV, and all from group V were treated in hospital.

TABLE 3
**Results of Multivariate Analysis***

| Variables | *P* | OR | 95% CI |
|---|---|---|---|
| Age, years | 0.014 | 1.038 | 1.008-1.069 |
| BMI | 0.023 | 0.945 | 0.900-0.992 |
| CHF | 0.051 | 1.679 | 0.998-2.825 |
| $FEV_1$, ≤40% of pred | 0.021 | 1.821 | 1.096-3.026 |

*BMI indicates body mass index; CHF, congestive heart failure; $FEV_1$, forced expiratory volume in 1 second; pred, predicted; OR, odds ratio; CI, confidence interval.

Of the items additional to the PSI that were included in the study, current smoking, alcoholism, and corticosteroid treatment were not associated with higher risk of death; nor was cavitated pneumonia associated with greater mortality. Mortality was significantly greater in patients with radiographic evidence of multilobular involvement (odds ratio [OR]=4.17; 95% confidence interval (CI), 1.09-15.89; *P*=.04), sepsis (OR=20; 95% CI, 2.46-199.38; *P*=.002), and inpatients that needed either invasive or noninvasive mechanical ventilation (OR=23.45; 95% CI, 5.08-108.07; *P*=.00004).

Eleven of the 88 COPD patients with pneumonia died, representing an overall mortality rate of 12.5%. The mortality rate was 8% (6/76) for CAP and 42% (5/12) for nosocomial pneumonias. Risk of mortality in nosocomial pneumonia was thus nearly 7 times higher than in CAP (OR=6.67; 95% CI, 1.65-26.93). Mortality by etiology was 4.6% (3/65) for unknown microbes, 21.4% (3/14) for gram-negative bacilli, 20% (1/5) for pneumococci, and 100% (2/2) for *S aureus* and fungi. Analysis of CAP mortality by PSI risk group showed no deaths for groups I, II, and III, 3.5% (1/28) for group IV, and 35.7% (5/14) for group V.

## Discussion

The main finding of our study was the high incidence of CAP in COPD patients, almost double the incidence in the general population adjusted for age. Considering that at the age at which COPD patients develop pneumonia the incidence in the general population is estimated to be approximately half[3] the overall rate of 55.1 pneumonias per year per 1000 patients we found for patients with COPD, the incidence we report for this population is clearly elevated. A high incidence of pneumonia was also found among patients with severe bronchial obstruction ($FEV_1$<40% of predicted), possibly explained by increased deterioration of pulmonary defense mechanisms, which leads to permanent bronchial obstruction. In fact airflow obstruction has been introduced as a possible risk factor for patients in an advanced stage of disease in SEPAR guidelines.[13] Our study showed that COPD patients with severe airflow obstruction were almost twice as likely to develop pneumonia than COPD patients with milder lung obstruction, including those who were older (OR=1.821; 95% CI, 1.096-3.026; *P*=.021).

Other factors associated with pneumonia were heart disease and low body mass index. Heart disease is a factor known to predispose a patient to pneumonia,[14] and body mass index has been associated with poor prognosis in COPD patients independently of airflow obstruction.[15] The fact that immunocompetent patients were selected for our study introduced a certain bias; however during the study period a considerable number of patients developed neoplasms. If factors associated with immunocompromise such as kidney failure and neoplasms had been considered, the effect of bronchial obstruction might have been reduced or hidden, particularly in patients with the comorbidity common among older patients. In a study performed by Saldías et al,[16] the incidence of comorbidity was greater among older adults.

Another significant finding was that over half the COPD patients who presented CAP corresponded to PSI risk groups IV and V—55.2% (42/76)—and that patients from group V as well as patients with nosocomial pneumonia had a very high mortality rate—35.7% and 42% respectively. Finally, certain factors not considered in the PSI, such as radiographic evidence of multilobular involvement, sepsis, and the need for invasive or noninvasive mechanical ventilation during hospitalization, indicated a greater risk of mortality in our COPD patients.

These results differ from previous results published for other series. Ruiz et al[17] compared CAP in patients with COPD and in patients without bronchial obstruction and found the former to be in higher risk classes even though the difference was not reflected in the mortality rate. The mortality they reported in patients in risk group V was 27%,[4] whereas in our study it was 38.5%. However, overall mortality for pneumonia in our study was 12.5%, higher than the maximum observed in the general population. One item not included in our study but which reflects a high risk of mortality is the need for intensive care, which is in turn related to a higher score on the Fine scale and a greater number of complications.[18]

Alcohol intake is not included in the PSI and did not influence outcome although other studies, such as the one carried out by Ruiz et al,[17] found an association between alcohol intake of more than 80 g per day and higher CAP mortality. Examining other factors not included in the PSI, El-Solh et al[19] found similar results to ours: an increase in mortality for sepsis and radiographic evidence of multilobular involvement, although it must be noted that this study was carried out on older patients (≥75 years) and overall mortality was 54.8%.

Menéndez et al[20] found a direct association between CAP mortality and treatment failure, which in turn was related to risk group and multilobular involvement. However, COPD was not a risk factor of treatment failure and did not therefore represent a determining factor of higher mortality in this study. In a study by Martínez-Moragón et al,[21] multilobular involvement was reported as more common in patients from nursing homes. These patients had a particular clinical profile for pneumonia, having greater age, comorbidity, and functional decline and consequently higher mortality.

The relation between etiology and mortality has not been adequately studied due to the small number of patients with pneumonia of known etiology. According to the guidelines of the Latin American Thoracic Society (ALAT),[22] mortality from pneumonia caused by enterobacteria or *S aureus* is 35% whereas in our series mortality was 21% (3/14) for gram-negative bacilli and 100% (2/2) for *S aureus*.

We think that more studies need to be undertaken in order to determine whether COPD, at least when disease is severe, is a factor related to higher mortality and should therefore be included in the risk scale. The studies published to date have been inconclusive and the results frequently inconsistent. Such studies will help decision making, as COPD is a prevalent disease in Spain.[10] Moreover, a patient's risk group could be a factor in determining treatment type or whether to hospitalize.[23,24] More studies might clarify whether the varying degrees of severity of COPD, or other mentioned aspects of pneumonia such as multilobular involvement or the need for mechanical ventilation, can be considered factors of poor prognosis and whether they should therefore be included in current applied risk scales.

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