ORIGINAL ARTICLES

Risk Factors for Increased Cost of Exacerbations of Chronic Bronchitis and Chronic Obstructive Pulmonary Disease

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OBJECTIVE: To identify what variables characterizing the patients, exacerbations, and treatment of chronic bronchitis and chronic obstructive pulmonary disease (COPD) are associated with a higher direct health cost.

METHOD: Observational pharmacoeconomic study of exacerbations of chronic bronchitis and COPD (of probable bacterial etiology, defined as Anthonisen types I or II). Direct health costs were assessed during 30 days of follow-up. Logistic regression was employed for statistical analysis, with calculation of the adjusted odds ratios (OR). An exacerbation cost greater than €150 was defined as the dependent variable.

RESULTS: Data on 1164 patients were collected by 252 physicians. Pharmacoeconomic data were complete in 947 patients (82.6%). In the first 30 days, 206 sought medical attention because of unsatisfactory response to treatment (21.8%), 69 (7.3%) attended the emergency room, and 22 (2.3%) were admitted to hospital. Overall, 101 exacerbations (10.7%) were classified as high cost (>€150). Continuous oxygen therapy (OR=7.58) and previous hospitalization (OR=2.6) were associated with high-cost exacerbations, whereas diagnosis of chronic bronchitis (OR=0.41) and treatment of the exacerbation with moxifloxacin or amoxicillin–clavulanic acid as opposed to clarithromycin (OR=0.38) were associated with low-cost exacerbations.

CONCLUSION: Treatment failure was reported for 21.8% of the patients with exacerbations of chronic bronchitis and COPD. Repeated medical visits and requests for complementary tests were the main factors responsible for increased cost. Variables associated with high-cost exacerbations were continuous oxygen therapy, previous hospitalization, and treatment with clarithromycin as opposed to moxifloxacin or amoxicillin-clavulanic acid.

Key words: *Chronic bronchitis. COPD. Exacerbations. Antibiotics. Costs. Pharmacoeconomics.*

Factores de riesgo de elevado coste de las agudizaciones de la bronquitis crónica y la EPOC

OBJETIVO: Identificar las variables de los pacientes, de las agudizaciones y del tratamiento de la bronquitis crónica (BC) y la enfermedad pulmonar obstructiva crónica (EPOC) que se asocian con un mayor coste sanitario directo.

MÉTODO: Estudio observacional y farmacoeconómico en pacientes con BC y EPOC con agudización de probable etiología bacteriana, definida por presentar 2 o más de los criterios de Anthonisen. Se siguió a los pacientes durante 30 días y se evaluaron los costes directos derivados de su atención. El análisis estadístico se efectuó mediante regresión logística con cálculo de las *odds ratio* (OR) ajustadas, considerando variable dependiente un coste de agudización superior a los 150 €.

RESULTADOS: Participaron 252 médicos que recabaron información sobre 1.164 pacientes. Se recogieron todos los parámetros farmacoeconómicos en 947 pacientes (82,6%). En los primeros 30 días, 206 acudieron por mala evolución (21,8%), 69 (7,3%) requirieron atención en urgencias y 22 (2,3%) precisaron ingreso. Se clasificaron como de coste elevado (> 150 €) 101 agudizaciones (10,7%). Las variables que se asociaron a un coste elevado fueron la oxigenoterapia continua (OR = 7,58) y la hospitalización previa (OR = 2,6), mientras que el diagnóstico de BC (OR = 0,41) y el tratamiento de la agudización con moxifloxacino o amoxicilina-ácido clavulánico, comparado con claritromicina (OR = 0,38), se asociaron a un coste bajo.

CONCLUSIÓN: Un 21,8% de los pacientes con agudización de la BC y EPOC fracasa, con lo que se genera un coste mayor, fundamentalmente por nuevas visitas médicas y solicitud de pruebas complementarias. Las variables que se asocian a una agudización de coste elevado son la oxigenoterapia continua, la hospitalización previa y el tratamiento con claritromicina comparada con moxifloxacino o amoxicilina-ácido clavulánico.

Palabras clave: *Bronquitis crónica. EPOC. Agudizaciones. Antibióticos. Costes. Farmacoeconomía.*

Introduction

Chronic pulmonary diseases, in particular chronic bronchitis and chronic obstructive pulmonary disease (COPD), are one of the main reasons for visits to a physician in primary health care. Studies done in Spain estimate that as many as 8% to 10% of the population

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over 40 years old may have COPD, and the proportion may be as high as 20% in men over the age of 65 years. In addition, given that increasing numbers of women are smokers, the prevalence of COPD is expected to increase among the general population in the coming years.[2] The course of both chronic bronchitis and COPD may be affected by episodes of worsening of respiratory symptoms known as exacerbations. Many of these exacerbations are caused by infections.

Effective treatment of infective exacerbations of chronic bronchitis and COPD requires administration of an antibiotic with an appropriate spectrum of action, an easy-to-follow dosage regimen, and a reasonable price. Given that health costs have increased inexorably in recent years while resources have remained necessarily limited, the economic aspects of the pharmacological treatments should be studied. Antibiotic treatment is an ideal field for pharmacoeconomic analysis because the outcomes of treatment regimens are quickly evident.[3] Studies already published suggest that pharmacoeconomic analyses are important for chronic bronchitis and COPD, and in particular, for the cost of exacerbations. Such analyses are even more relevant given that patients with COPD suffer on average 2 exacerbations, 90% of which are treated with antibiotics, and that 10% of the patients worsen and are admitted to hospital.[4]

In Spain, the cost of this disease has not been extensively investigated. Two studies found that direct annual costs ranged on average from €900 to €1600 and highlighted that hospital care of exacerbations represented between 40% and 50% of the total cost.[5,6]

According to a pharmacoeconomic study of 2414 exacerbations in sufferers treated as outpatients, the average direct cost of an exacerbation was €134.1, but the cost of therapeutic failure was €402.7.[7] Thus, 63% of the total cost associated with managing the exacerbation was derived from treatment failure. It is instructive to compare these figures with the mean cost of antibiotic treatment in this same study—just €31 corresponding to 18% of the total cost of the exacerbation. A preliminary analysis of the EFEMAP study found that the mean cost per exacerbation was €118.6 and that therapeutic failure accounted for 44.2% of the total cost.[8] The present study aimed to identify the variables of underlying pulmonary disease, severity of the exacerbations, and treatment that might be significantly and independently related to a higher direct health cost in treatment of chronic bronchitis and COPD exacerbations.

Method

This was a multicenter, observational, pharmacoeconomic study in a primary health care setting of a population of patients with controlled chronic bronchitis and COPD. The study was carried out between February 2001 and May 2002 in centers throughout Spain. A nonrandom sample of consecutive cases was taken. Investigators were asked to include the first unselected 10 adult patients aged over 40 years who had attended their clinics and who were diagnosed with a chronic bronchitis or COPD exacerbation of probable bacterial origin. Chronic bronchitis was diagnosed if the patient had presented with productive cough for at least 3 months of the year for 2 consecutive years. COPD was diagnosed upon finding irreversible airway obstruction characterized by a forced expiratory volume in 1 second (FEV_1) less than 80% of the theoretical value and a ratio of FEV_1/forced vital capacity (FVC) below 70% in stable phase.[9] Sources of error in spirometric readings were minimized as far as possible by recalculating the values for FEV_1/FVC, FEV_1%, and FVC% from anthropometric data and absolute values of FEV_1 and FVC with the formulae of Roca el al.[10] Patients with bronchial asthma, cystic fibrosis, bronchiectasis arising from processes other than COPD, and neoplasms were excluded; patients meeting the criteria for admission to hospital were also excluded. The definition of an exacerbation was based on symptoms, according to the criteria of Anthonisen et al.[11] In short, a patient had an exacerbation of probable bacterial origin when at least 2 of the following symptoms were present: increased dyspnea, increased sputum volume, and/or increased purulence of the sputum. The exacerbations were classed as type II when 2 of these symptoms were present and as type I when 3 were present.[11]

After diagnosis of the exacerbation, the physician was free to prescribe one of the following 3 antibiotic treatments according to current guidelines[12]: combination of 500 mg of amoxicillin and clavulanic acid every 8 hours for 10 days; 400 mg/day of moxifloxacin for 5 days; or 500 mg of clarithromycin every 12 hours for 10 days. A visit was arranged for all patients after 30 days to assess the course of the exacerbation.

Data Collection Method

All data were collected with a specifically designed form in electronic format. This form included information on demographic variables, respiratory risk factors such as how much the patient smoked, prior respiratory infections, comorbidity, characteristics of the respiratory disease according to the type and intensity of symptoms and exacerbations the previous year, dyspnea grade (0 to 4 according to the Medical Research Council scale[13]), usual medication, characteristics of the exacerbation, and treatment administered. The form was loaded onto a Hewlett Packard Jornada 545 color Pocket PC with a 32 bit processor, 16 MB of RAM, and 16 MB of ROM. Data were transmitted to a single database over a telephone line with a 56 K 33.3 V CompactModem for the Pocket PC. The data transferred did not include any information that might identify individual participants and violate confidentiality. The information provided by all the physicians who participated in the study was gathered on the server in a single database administered by the data processing center (Biomedical Systems Group S.A., Barcelona, Spain). No hardcopy versions of study documentation were used during the study. The data processing center provided the investigators with an e-mail address and a toll-free telephone number (900 prefix) for clarification of doubts about the questionnaire, computer, or data transmission. A pilot study was run to check that the system worked properly.[14]

Pharmacoeconomic Analysis

The costs assessed were the so-called "direct costs," that is, those that actually arise from the use of health care resources.

Resource consumption was determined by the cost of treating the exacerbation, as well as the cost arising from treatment failure. The estimated cost was therefore limited to the following elements: antibiotic treatment used, new outpatient clinic visit to the primary health care physician or pulmonologist, hospital visit to the pulmonologist, visit to the emergency room, hospital stay, admission to the intensive care unit, chest x-rays, spirometry, blood testing, electrocardiogram, and arterial blood gas analysis. The Spanish health costs database (SOIKOS) was used to calculate all these costs,[14-16] as described in previous studies (Table 1).[5-8] The recommended retail price for each drug[17] was used to calculate the costs associated with pharmacological treatment. The reference prices used correspond to 2002, when the study was conducted. The process followed to calculate total costs has been presented in greater detail in a previous publication.[8]

TABLE 1
Estimated Costs of Health Resources Considered in This Study*

Resource	Cost (€)
Medications	Prices in 2002
Health care	
Visit to the family physician	7.11
Visit to the pulmonologist in a primary health care setting	20.21
Visit to the hospital pulmonologist	67.92
Visit to the emergency room	97.68
Admission to hospital (per day)	312.73
Stay in the ICU (per day)	1091.72
Diagnostic tests	
Chest x-ray	16.74
Spirometry	34.56
Blood testing	15.28
Electrocardiogram	19.16
Arterial blood gas analysis	23.17

*ICU indicates intensive care unit
Source: SOIKOS database.[14-16]

Statistical Analysis

The study variables were analyzed descriptively before applying the Student *t* test and Snedecor *F* test (analysis of variance) to compare means and the χ^2 test to compare categorical variables. In a second phase of the analysis, we carried out a logistic regression of the independent variables analyzed. The dependent study variable was high cost, defined as a cost greater than €150. The cutoff point was chosen using the mean cost of an exacerbation obtained in the present study[8] and the cutoff points obtained in a previous study carried out in Spain.[7]

A regression model was constructed to identify independent variables significantly associated with high cost. A randomly selected subsample of 90% of the individuals included in the study was used for the initial model (development model), which was checked with data from the remaining 10% of the population (validation model). Selection of patients for these models was done by randomly assigning a number between 0 and 1 to each patient. Data from patients assigned a number below 0.90 were included in the first model whereas data from the remaining patients were used in the validation model.

For the results of the model to be useful in clinical practice, we only included well-defined, widely used variables that are easy to obtain. Radiographic, microbiological, and analytical variables that are not usually used in outpatient care were not included. The candidate variables were age, sex, smoking habit (current smoker vs ex-smoker or nonsmoker), years with the disease, presence of not of chronic bronchitis and comorbidity (coded as absence or presence of diseases such as ischemic heart disease, diabetes, or hypertension, selected for having a prevalence of 5% or more), severity of the underlying disease (quantified according to dyspnea grade), number of exacerbations in the previous year, severity of the exacerbation (type I or II), and treatment with oral corticosteroids, antibiotics (moxifloxacin, clarithromycin, or amoxicillin-clavulanic acid), and drugs belonging to certain other therapeutic groups. Lung function variables were not included because they were only available for 52.7% of the patients.

A variable was included in the model if it was associated with high cost ($P<.10$) and provided a value for that variable was available for at least 5% of the population. Correlations between regression coefficients were used to check for colinearity.[18] A variable was considered significant when the absolute value for *r* was greater than 0.7. The variables were then eliminated from the model one by one according to their likelihood ratio. After eliminating all variables that did not prove relevant from the model, the goodness of fit of the calibration was checked with the Hosmer-Lemeshow test.[15] The discrimination was assessed using the receiver operating characteristics (ROC) curve.[18]

A difference was considered significant if *P* was less than .05. The SAS software package (SAS Institute, Cary, SC, USA), version 7.0 for Windows 95, was used for the analysis.

Results

Study Population

Information on 1164 patients with exacerbations of probable bacterial origin, defined as Anthonisen type I or II, was collected by 252 family physicians. Most patients were men (81%) and the mean (SD) age of the population was 68.7 (9.4) years. In the previous year, 71.8% of the patients had suffered 2 or more exacerbations.

Overall, 311 exacerbations (26.7%) were classified as type I and 853 (73.3%) as type II. Complete information for pharmacoeconomic assessment was obtained for the 947 patients (82.6%) who attended the follow-up visit after 1 month. The antibiotic treatment administered was amoxicillin in combination with clavulanic acid in 294 patients (31%), moxifloxacin in 400 patients (42.4%), and clarithromycin in 253 patients (26.8%). Clinical and demographic characteristics and exacerbation severity did not differ significantly among the 3 treatment groups (Table 2).

Pharmacoeconomic Assessment

In the month after initiation of treatment, 206 patients (21.8%) needed a new outpatient visit due to unsatisfactory response to treatment or incomplete resolution of symptoms, 69 (7.3%) visited the emergency room, and 22 (22.3%) were admitted to hospital.

TABLE 2
Characteristics of Patients According to Treatment Group (n=947)*

	All Patients	Moxifloxacin (n=400)	Amoxicillin-Clavulanic Acid (n=294)	Clarithromycin (n=253)	*P*†
Patient characteristics					
Age, years	68.8 (9.2)	68.7 (10.2)	69.3 (10.4)	67.9 (11.5)	.79
No. of men, %	766 (80.9%)	334 (83.5%)	239 (81.3%)	193 (76.3%)	.079
Duration in years of CB/COPD	12.3 (7.9)	12.5 (8.5)	12.1 (7.1)	12.3 (7.8)	.99
>2 comorbidities, %	25.5	24.1	25.3	27.1	.53
Smokers and ex-smokers, %	78.4	79.2	81.2	74.3	.335
Packet-years	37.1 (24)	42.3 (26.4)	42.6 (25.2)	43.7 (24.9)	.58
Lung function					
FVC, mL	2539.2 (853)	2561 (925)	2553 (918)	2557 (935)	.78
FVC%	67.6 (15.9)	67.5 (153.9)	67.5 (19)	68 (16.1)	.46
FEV_1, mL	1487.5 (628)	1499.8 (655)	1504 (640)	1482.4 (673)	.33
FEV_1%	51.3 (13.9)	50.5 (14.8)	52.4 (13.5)	51.7 (16.1)	.53
FEV_1/FVC	58.2 (13.1)	57.7 (14.2)	59 (15.1)	58.2 (14.4)	.51
Exacerbations in previous year	2.5 (1.7)	2.5 (1.6)	2.5 (1.9)	2.44 (1.8)	.54
Characteristics of the exacerbations					
Anthonisen type I, %	27.3	26.6	28.4	27	.10
Treatment with oral corticosteroids, %	24.2	26.2	23.2	23.3	.45

*Data presented as mean (SD), unless otherwise specified.
BC indicates chronic bronchitis; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.
†Values with respect to comparison between the 3 groups by the Kruskal-Wallis test or the χ^2 test as appropriate.

The mean health cost of the exacerbations analyzed was €118.58 (95% confidence interval [CI], €92.2-€144.9). The cutoff point between high- and low-cost exacerbations was set at €150. Table 3 compares the demographic and clinical characteristics and the treatments administered to the patients with exacerbations, according to whether the exacerbations were low or high cost. It was observed that high-cost exacerbations corresponded to older patients with more severe underlying dyspnea and lower FEV_1%. The mean FEV_1 of patients with high-cost (>€150) exacerbations (47.9%) was significantly lower than that of patients with low-cost (<€150) exacerbations (51.7%; $P<.05$). Treatment with clarithromycin was more often associated with high cost compared to the other 2 treatment options ($P<.001$).

The results of the multivariate analysis with high cost (>€150) as the dependent variable are presented in Table 4. The variables predictive of high cost were continuous home oxygen therapy, with an odds ratio (OR) of 7.58 (95% CI, 4.6-12.5), and previous admission to hospital (OR=2.62; 95% CI, 1.6-4.2). In contrast, diagnosis of chronic bronchitis and treatment with moxifloxacin or amoxicillin-clavulanic acid compared to clarithromycin were associated with low cost.

COPD diagnosis was confirmed by spirometry in 614 patients (52.7%). Mean (SD) FEV_1 was 51.4% (14%), indicating a mainly moderate deterioration in lung function. In this subgroup of patients, the variables associated with high cost were also continuous home oxygen therapy (OR=6.27; 95% CI, 3.2-1.2) and previous admission to hospital (OR=2.14; 95% CI, 1.1-3.9). Once again, treatment with moxifloxacin or amoxicillin-clavulanic acid was associated with low-cost exacerbations compared to clarithromycin (OR=0.21; 95% CI, 0.1-0.4). In addition, there was a trend towards a greater association of moxifloxacin with a low-cost exacerbation compared to amoxicillin-clavulanic acid in COPD patients, though this trend was not statistically significant (OR=0.47; 95% CI, 0.21-1.04).

According to the Hosmer-Lemeshow test, the goodness of fit was satisfactory and the area under the ROC curve indicated that discrimination was acceptable (Table 4).

Discussion

Approximately 22% of the patients required further medical attention in the month after starting treatment in order to achieve full resolution of their exacerbation. Of these patients, 7% visited the emergency room and 2% required admission to hospital. These findings agree with previous studies that have shown that patients with a COPD exacerbation often return to their physician because symptoms persist despite receiving supposedly correct treatment. According to McFarlane et al,[19] up to 25% of the patients consulted their family physician again within a month due to inadequate clinical improvement. Moreover, most were prescribed new courses of antibiotics. The results were similar in another extensive study of 2414 patients in Spain: 21% of the patients required further medical attention due to relapse.[20] Adams et al[21] studied 372 exacerbations treated in an outpatient setting and found a failure rate of 22% after 14 days. In the United States of America, a study of 140 patients with COPD monitored after visiting the emergency room for an exacerbation also found a therapeutic failure rate of 21% after 14 days.[22]

It is essential to identify the clinical situations or risk factors associated with greater cost of treatment of chronic bronchitis or COPD exacerbations. This would allow strategies to be drawn up to optimize the limited resources available. Use of continuous home oxygen therapy was associated with a greater risk of a high-cost

TABLE 3
Characteristics of the Patients According to the Cost of the Exacerbations*

Variables	All Patients (n=947)	Cost <€150 (n=846)	Cost >€150 (n=101)	*P*
Sex, male	766 (80.9%)	681 (80.5%)	85 (84.2%)	.37
Age, years	68.8 (9.2)	68.6 (9.1)	70.6 (9.1)	.016
Active smoker	219 (23.2%)	193 (22.8%)	26 (25.7%)	.51
Packet-years	37.1 (24)	37.2 (25)	36.3 (26.1)	.55
Duration in years of CB/COPD	12.3 (7.9)	12.3 (8)	12.7 (6.6)	.19
Comorbidity	520 (55%)	463 (54.7%)	57 (57%)	.66
Chronic bronchitis	765 (80.8%)	690 (81.6%)	75 (74.3%)	.07
Severity of underlying dyspnea				
0 or 1	464 (49%)	431 (93%)	33 (7%)	<.0001
2	344 (36.3%)	306 (88.9%)	38 (11.1%)	
3 or 4	138 (14.6%)	104 (75.6%)	34 (24.4%)	
Lung function				
FVC, mL	2539.2 (853)	2541.4 (859)	2522.2 (808)	.96
FVC%	67.6 (15.9)	67.9 (15.9)	65.7 (16.3)	.25
FEV_1, mL	1487.5 (628)	1496.6 (636)	1418.5 (569)	.43
FEV_1%	51.3 (13.9)	51.7 (13.9)	47.9 (13.3)	.023
No. of exacerbations in the previous year				
0 or 1	267 (28.2%)	247 (92.5%)	19 (7.5%)	.046
≥2	680 (71.8%)	598 (88%)	82 (12%)	
Admissions in the previous year	0.29 (0.6)	0.23 (0.6)	0.73 (0.8)	<.0001
Treatment				
Short-acting β_2-agonists	643 (67.9%)	568 (67.2%)	73 (73.3%)	.21
Long-acting β_2-agonists	665 (70.2%)	587 (69.4%)	78 (77.2%)	.10
Ipratropium bromide	584 (61.7%)	520 (61.5%)	64 (63.7%)	.67
Inhaled corticosteroids	585 (61.8%)	513 (60.6%)	72 (72.3%)	.021
Home oxygen therapy	103 (10.9%)	6 (7.2%)	42 (41.6%)	<.0001
Anthonisen type				
I	259 (27.4%)	234 (90.2%)	25 (9.8%)	.57
II	688 (72.6%)	611 (88.9%)	77 (11.1%)	
Antibiotic				
Moxifloxacin	400 (42.2)	372 (93.0)	28 (7)	<.0001
Amoxicillin-clavulanic acid	294 (31)	269 (91.8)	25 (8.2)	
Clarithromycin	253 (26.8)	204 (80.6)	49 (19.4)	

*Values expressed as mean (SD) or as number of patients (percentage).
BC indicates chronic bronchitis; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.
The Student *t* test and the Snedecor *F* test (analysis of variance) were used for comparison of means and the χ^2 test for comparison of categoric variables.

TABLE 4
Variables Included in the Model for High Direct Health Costs (>€150 per Exacerbation)*

Variables	Estimated Adjusted OR	95% CI
All patients†		
Home oxygen therapy	7.58	4.62-12.46
Previous admission to hospital	2.62	1.64-4.18
Chronic bronchitis	0.41	0.24-0.68
Moxifloxacin versus clarithromycin	0.38	0.23-0.63
Moxifloxacin versus amoxicillin-clavulanic acid	0.89	0.52-1.55
Patients with COPD‡		
Home oxygen therapy	6.27	3.22-12.23
Previous admission to hospital	2.14	1.15-3.96
Moxifloxacin versus clarithromycin	0.21	0.10-0.43
Moxifloxacin versus amoxicillin-clavulanic acid	0.47	0.21-1.04

*COPD indicates chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.
†Hosmer-Lemeshow test for goodness of fit, *P*=.503.
Area under the receiver operating characteristics (ROC) curve: 0.64.
‡Hosmer-Lemeshow test for goodness of fit, *P*=.634.
Area under the ROC curve, 0.72.

exacerbation. A previous study of 107 patients treated in an outpatient setting also identified continuous home oxygen therapy and the previous frequency of exacerbations as the only independent factors that determined treatment failure in 83% of the patients.[23] These results are not surprising because continuous home oxygen therapy is a marker of severity of the underlying disease. Previous admission to hospital is also expected to be associated with greater risk of a high-cost exacerbation. In both cases, the patients have more severe disease and a greater risk of failure and admission to hospital. Recently, Oostenbrink and Rutten-van Mölken[24] observed how the cost of exacerbations was up to 7 times greater in patients with severe COPD than in those with moderate disease. These exacerbations in patients with moderate disease were in turn almost 7 times more expensive than in those with mild disease. In this study, the definition of severity was based on the use of resources, such that patients with severe disease were those that required hospital care; therefore we could not identify risk factors of high cost from these patients' data. It should

be remembered that the mean FEV_1 in patients with COPD included in our study was 51.3% and that the mean FEV_1 observed in the group of patients with exacerbations and a cost more than €150 was significantly lower (47.9%). Pathogens are known to be isolated more often from patients with more severe pulmonary disease, and the microorganisms that are usually isolated are those that are harder to eradicate, such as *Haemophilus influenzae* and gram-negative bacteria.[25] On the other hand, diagnosis of chronic bronchitis is associated with a low-cost exacerbation. Chronic bronchitis is the mildest of the bronchial diseases caused by smoking and many sufferers have normal lung function. This is important because it should be remembered that when lung function is retained, the probability of bacterial infection decreases substantially,[25] as does the risk of therapeutic failure.

A novel finding was the variation in outcomes according to the antibiotic treatment used. An exacerbation costing more than €150 was reported in 19.4% of the patients treated with clarithromycin, compared to 8.2% in the group treated with amoxicillin-clavulanic acid, and 7% in the group treated with moxifloxacin. In principle, the costs of acquiring the antibiotics should be the first consideration when different drugs have the same therapeutic outcome, when the possibility of resistance is the same, and when the incidence of adverse effects is similar. Apart from these considerations, we should also bear in mind aspects other than just the cost,[26] as demonstrated by the preliminary analysis of the results of the EFEMAP study, which showed that exacerbations of chronic bronchitis and COPD treated with clarithromycin were associated with a higher mean cost than those treated with amoxicillin-clavulanic acid or moxifloxacin.[8] The preceding study only quantified the direct cost associated with the use of each of the antibiotics, whereas the present analysis attempted to identify which characteristics of the patient, the exacerbation, or treatment were associated with a higher cost. Even after including all the variables relating to the severity of the underlying disease and the severity of the exacerbation in the multivariate model, we found that antibiotic therapy with moxifloxacin or amoxicillin-clavulanic acid was significantly and independently associated with cost savings compared to clarithromycin. This is so because of savings resulting from avoiding further visits or hospital care thanks to the better efficacy of moxifloxacin and amoxicillin-clavulanic acid, even though the 3 treatment groups were perfectly balanced for all demographic, clinical, and functional characteristics, as well as for severity of the exacerbation and concomitant treatments.[8] In an observational study in the United States of America, the outcomes of 372 exacerbations varied according to the antibiotic treatment used. The failure rate for patients who received amoxicillin was significantly higher than for other patients (OR for amoxicillin failure, 3.37; 95% CI, 1.44-8.13), whereas the use of other antibiotics provided greater protection against therapeutic failure (OR=0.28; 95% CI, 0.15-0.53).[21] Likewise, the lower cost associated with use of moxifloxacin may be related to the faster resolution, as observed in the EFEMAP study[27,28] and also in an earlier study in outpatients with exacerbations of moderate-severe COPD.[29] The slow resolution of symptoms could be interpreted by the patient and the physician as a lack of efficacy and so lead to further visits and diagnostic tests and/or unnecessary changes in treatment. Hospitalization is the item that most determines the cost of health care, such that the factors of high cost generally coincide with risk factors for hospital admission. In the present study however, the rate of hospitalization was extremely low and showed no significant differences among the 3 treatment groups.[8] Therefore, drug costs and whether further visits and treatments were required because of unsatisfactory response to the initial treatment also bore a strong relation to high cost.

Greater severity of underlying disease, as indicated by worse underlying dyspnea, was significantly related to high cost, but this variable was not significant in the regression model. This is probably because other variables of severity such as continuous home oxygen therapy and previous admissions were stronger risk markers.

It is important to highlight that we tried to include only patients who suffered an exacerbation that was of probable bacterial origin, according to the criteria of Anthonisen et al.[11] The advantages of using amoxicillin-clavulanic acid or moxifloxacin were observed in this population, which on average showed moderate lung-function deterioration and at least 2 main symptoms of exacerbation. The use of antibiotics in patients with very mild disease or with only 1 symptom of exacerbation (Anthonisen type III) is generally not recommended[30] and the possible superiority of some antibiotics over others has certainly not been demonstrated in such patients.

In conclusion, treatment of exacerbations of chronic bronchitis and COPD was associated with high costs, especially in patients with severe disease who used continuous home oxygen therapy and who had been admitted to hospital previously. Treatment with moxifloxacin or amoxicillin-clavulanic acid was associated with a lower cost than treatment with clarithromycin. The pharmacoeconomic data should be born in mind when drawing up guidelines for the treatment of exacerbations of chronic bronchitis and COPD in primary health care.

APPENDIX

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