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Factors associated with relapse after ambulatory treatment of acute exacerbations of chronic bronchitis

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Factors associated with relapse after ambulatory treatment of acute exacerbations of chronic bronchitis. M. Miravitlles, C. Murio, T. Guerrero, on behalf of the DAFNE Study Group. ©ERS Journals Ltd 2001.

ABSTRACT: This study aimed to identify the risk factors for relapse after ambulatory treatment of acute exacerbations of chronic bronchitis (AECB) that can easily be used in a primary care setting.

Data were prospectively collected on 2,414 ambulatory patients with AECB from 268 general practices located throughout Spain. A multivariate model to identify risk factors independently associated with failures was developed and validated from the information recorded at the inclusion visit and at 30-days follow-up visit.

A total of 507 patients relapsed (21%); of these, 84 required admission (16.5%). The multivariate model for prediction of the risk of relapse included 2,414 cases: 1,689 for the developmental sample and 725 in the validation sample. The model obtained contained three readily-obtainable variables: ischaemic heart disease (odds ratio (OR) = 1.63; 95% confidence interval (CI) = 1.07 – 2.47), degree of dyspnoea (OR = 1.31; 1.14 – 1.50) and number of visits to the general practitioner the previous year (OR = 1.07; 1.04 – 1.10). The model calibrated well in developmental and validation samples (goodness-of-fit tests: p = 0.295 and p = 0.637, respectively). Severity of the exacerbation was not associated with increased risk of relapse in either univariate or multivariate analysis.

The present results suggest that baseline characteristics of the patients such as degree of dyspnoea, coexisting ischaemic heart disease and number of previous visits to the general practitioner for respiratory problems are strongly associated with increased risk of relapse after ambulatory treatment of acute exacerbations of chronic bronchitis. In contrast, exacerbation severity was not associated with clinical failure. Guidelines for management of acute exacerbations of chronic bronchitis should consider such risk factors and advocate intensive broad spectrum treatment and closer follow-up of patients exhibiting them.

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A significant number of smokers will develop chronic cough and sputum production. The chronic and progressive course of the disease is often aggravated by short periods of increasing symptoms, particularly increasing cough, dyspnoea and production of sputum which can become purulent. The majority of these exacerbations are produced by bronchial infection and, if frequent, have been demonstrated to have a negative impact on quality of life in patients with chronic bronchial disease [1]. Furthermore, acute exacerbations are the most frequent cause of hospital admission and death among patients with chronic lung disease [2].

Most studies consistently show a failure rate of ambulatory treatment of exacerbations that ranges from 12 – 26% [3 – 6]. Since relapse after initial treatment for acute exacerbation may lead to prolonged disability, a new course of antibiotics, an emergency visit or even hospital admission, it is crucial to identify patients most at risk for relapse. Identification of risk factors for failure of ambulatory treatment may permit the implementation of more aggressive broad spectrum treatment and closer follow-up. In a further step, risk factors associated with relapse should be incorporated into the management guidelines to aid general practitioners in identifying at-risk patients.

A cohort of patients with exacerbated chonic bronchitis was identified on a nationwide basis and was prospectively followed for 1 month to investigate the rate of failure and identify risk factors associated with relapse after ambulatory treatment of the exacerbation. This study's modelling goal was to develop and validate one simple system for estimating the probability of relapse after ambulatory treatment of an exacerbation of chronic bronchitis based on data collected in clinical records obtained at the visit to the general practitioner (GP).

Method

Study design

This is a prospective study on ambulatory patients with exacerbated chronic bronchitis in a primary care setting. The study was conducted between December 1, 1996 and April 30, 1997 in 268 general practices located throughout Spain and selected by regionally-stratified sampling. Information was sought on the first 10 unselected consecutive adults seen for exacerbated chronic bronchitis.

Diagnosis of chronic bronchitis was based on productive cough for at least 3 months in two consecutive yrs [7]. The degree of dyspnoea while in stable phase was used to classify the severity of the underlying disease and was assessed using the scale of MAHLER *et al.* [8]. Diagnosis of acute exacerbation was based on the presence of any combination of the following symptoms: increased dyspnoea, increased production and purulence of sputum which led to a change or increase in treatment. Severity of the exacerbation was classified using ANTHONISEN *et al.* [9] criteria: exacerbations presenting with any one of the previously mentioned symptoms were classified as type 3, those with two symptoms as type 2, and those with all three symptoms as type 1. Exclusion criteria included diagnosed cystic fibrosis, asthma or severe bronchiectasis.

All information relevant to the study was collected by GPs at the time of the patient's medical visit. Since this was an observational study aimed at identifying current practice and real failure rates, not under experimental conditions, treatment of the exacerbation was left to the criteria of the attending physician. Patients were rescheduled to see their GP 1 month after the first visit in all cases, or as requested in case of persistence or increase in symptoms. Relapse was defined as an unscheduled visit to the GP before 1 month owing to persistence or increase in symptoms and which led to either a change in drug prescription, an emergency visit or an admission to hospital.

Sample selection

A regression model was constructed to identify variables independently and significantly associated with relapse. The model was constructed using a randomly-selected subsample of 70% of the subjects included (developmental model). The model obtained was tested with data derived from the remaining 30% of the total population (validation sample). Developmental and validation samples were created by assigning each patient a random number between 0 and 1. Patients with a random number of 0.70 or lower formed the developmental sample and the remaining patients formed the validation sample.

The aim of the model was to accurately reflect the relapse experience of the patient sample while containing the minimum number of variables necessary to calibrate and discriminate well in the developmental and validation samples. Only clearly definable and reliably obtained terms were included and the use of laboratory values, radiological examinations and measurements, which may not be performed as part of routine patient care, were avoided. Candidate variables to be included in the model were: age, sex, body mass index (BMI) calculated as $kg \cdot m^{-2}$, smoking habits (active smoker *versus* non- or exsmoker), presence or absence of chronic mucus hypersecretion (CMH) defined as emission of >30 mL of sputum daily, and comorbidity (0 = no, 1 = yes) for any of the following: ischaemic heart disease, diabetes mellitus or hypertension, chosen by presenting a prevalence of 5% or greater of the study population, severity of the underlying disease quantified by the degree of dyspnoea, number of visits to the GP the previous year for respiratory symptoms, severity of the exacerbation based on classification as types 1, 2 or 3, and treatment with oral steroids. Since all but 34 patients (1.4%) received broad spectrum antibiotics, the use of antibiotics was not included as a variable in the model.

Statistical analysis

The association of categorical independent variables with failures was assessed by the Chi-squared test, and the significance of continuous variables was assessed with unpaired t-test and Wilcoxon's rank sum tests. Variables were eligible for entry into a multiple logistic regression model if they were significantly associated with failures at a p-value <0.25 and $\geqslant 5\%$ of the population exhibited that factor. Correlations (r) among the regression coefficients were used to screen for multicollinearity [10]. Absolute values of $r>0.7$ were considered significant. The κ statistic was used to assess inter-rater reliability of variables. Estimated coefficients and their SEMS were calculated using the method of maximum likelihood. Variables were eliminated from the model one at a time based on likelihood ratio tests.

When all statistically nonsignificant ($p>0.05$) variables had been eliminated from the multivariate model, calibration was assessed using the HOSMER-LEMESHOW [11] goodness-of-fit test. This test evaluates the degree of correspondence between a model's estimated probability of failure and the actual failure rate of patients over groups spanning the entire range of probabilities.

Discrimination was assessed using the area under the receiver operating characteristic (ROC) curve [12] to evaluate how well the model distinguished patients who relapsed from patients who did not. The statistic represents, for all possible pairs of patients, the proportion in which the patient who relapsed had a higher probability of relapse than the patient who did not. All the data were analysed using the Statistical Analysis System (SAS) 6.04 (SAS Institute, Cary, NC, USA).

Results

Data were collected from 2,414 individuals with exacerbated chronic bronchitis. Characteristics of the patients are described in table 1. Treatment administered for acute exacerbations included antibiotics in 98.6% and oral corticosteroids in 25% of cases. Coexisting respiratory medication included short-acting β_2-agonists in 56% of cases, inhaled

Table 1. – Characteristics of the population included in the study and univariate analysis of variables possibly associated with relapse

Variable	Total population	Success	Relapse	p-value
Subjects n	2414	1907	507	
Males %	74.2	74.8	74.1	0.785
Age yrs	67.1±10.3	66.9±10.1	68.1±10.2	0.022
BMI kg·m^{-2}	27.4±4.1	27.3±4.0	27.4±4.2	0.388
Active smokers %	20.1	19.9	20.7	0.207
Pack-yrs	41.7±27.0	40.7±26.7	43.1±25.8	0.139
Exacerbations previous year	3.0±2.2	2.9±2.2	3.4±2.1	<0.0001
Visits to the GP the previous year	5.3±4.3	4.9±3.8	6.6±5.1	<0.0001
Evolution of the disease yrs	12.6±8.2	12.3±8.1	13.9±8.5	0.0007
CMH %	40.9	40.0	44.1	0.095
Hypertension %	34.1	33.6	35.7	0.391
Diabetes mellitus %	14.2	13.5	15.9	0.153
Ischaemic heart disease %	8.5	7.1	11.8	0.002
Exacerbation %				
type 1	49.1	48.4	51.8	0.262
type 2	34.6	35.4	31.7	
type 3	16.2	16.1	16.5	
Dyspnoea %				
degree 0	9.0	10.0	5.4	0.001
degree I	40.2	42.4	31.9	
degree II	32.4	31.6	35.5	
degree III	14.5	13.4	18.5	
degree IV	3.8	2.5	8.6	

Data are presented as percentages or mean±SD. BMI: body mass index; GP: general practitioner; CMH: chronic mucus hypersecretion. Exacerbation types and dyspnoea degrees are defined in [9] and [8], respectively.

corticosteroids in 46.7%, long-acting β_2-agonists in 41.4%, theophyllines in 43.5%, mucolytic agents in 38.2%, ipratropium bromide in 26.9% and home oxygen therapy in 11.3%.

A total of 507 patients (21%) suffered a relapse of the exacerbation; in 262 cases (51.6%) the relapse was resolved with an unscheduled visit and a change of treatment, but in 161 cases (31.7%) patients required attention in an emergency department and 84 (16.5%) were finally admitted to hospital. Characteristics of patients who relapsed and those who did not are presented in table 1.

Multivariate model

The total population was randomly divided into two samples: 1,689 individuals for the developmental sample and 725 for the validation sample. The overall rate of patients who relapsed was 21.0%; 21.0% in the developmental sample and 21.0% in the validation sample. Results of bivariate analysis of independent variables are also shown in table 1. Mean age was 68.1 yrs among patients who relapsed and 66.9 yrs among patients who did not. Number of exacerbations the previous year was 3.4 in those who relapsed and 2.9 in those who did not. Patients who relapsed had seen their GP more often the previous year (6.6 times *versus* 4.9) and more frequently had ischaemic heart disease (11.8% *versus* 7.1%). Each of these variables was selected as showing a significant difference of $\geqslant 0.25$. Conversely, the severity of the exacerbation was not selected for incorporation into the model, since it failed to show a significant relationship with relapse in univariate analysis ($p > 0.25$).

A significant correlation was observed between the number of exacerbations the previous year and the number of visits to the GP for respiratory problems (Spearman's $r = 0.71$; $p < 0.0001$); thus, the number of visits to the GP was selected to enter the model. Similarly, the use of oral steroids correlated with disease severity, measured by the degree of dyspnoea at baseline ($r = 0.82$; $p < 0.0001$); since the use of corticosteroids is the consequence of the severity and not *vice versa*, the degree of dyspnoea was the variable chosen for the model.

Multiple logistic regression modelling in the developmental data set resulted in a model containing three variables. Table 2 presents the estimated logistic regression coefficients, estimated SEMs, adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the adjusted ORs for the final model for relapse. The presence of ischaemic heart disease had an OR of 1.63, which signifies that a patient that had this condition would be 1.63 times as likely to relapse as another patient that did not have this disease. The degree of dyspnoea and the number of visits to the GP the previous year also had a significant association with relapse.

The HOSMER-LEMESHOW [11] goodness-of-fit test indicated that the model was well calibrated ($p = 0.295$). In this test, a high p-value indicates that the model is performing well, which means that no large discrepancy is found between observed and expected rates of relapse. When the model was applied to the validation data, the area under the ROC curve was 0.633 and the p-value for the goodness-of-fit 0.637, indicating that the model validated well, especially by demonstrating good calibration and acceptable discrimination.

Table 2. – Variables in the model for relapse with their estimated coefficients (β) standard errors of the mean (SEMs), adjusted odds ratios (ORs), and 95% confidence intervals (CI) for the adjusted ORs

Variable	β	SEM	Estimated adjusted OR	95% CI
Constant	-2.2569	0.1498		
Degree of dyspnoea	0.2722	0.0691	1.313	1.14 – 1.50
Ischaemic heart disease	0.4898	0.2127	1.632	1.07 – 2.47
Visits to the GP the previous year	0.0726	0.0148	1.076	1.04 – 1.10

GP: general practitioner.

Discussion

The present findings show that severity of the underlying disease, classified by the degree of baseline dyspnoea, number of visits to the GP the previous year and coexistence of ischemic heart disease, are factors independently associated with increasing risk of relapse after ambulatory treatment for acute exacerbations of chronic bronchitis (AECB). However, the severity of the present exacerbation did not influence prognosis. From these results it can be speculated that the patient′s functional status is crucial for establishing the risk of relapse of respiratory symptoms.

To the authors′ knowledge, this is the largest prospective study conducted in patients with AECB. This study aimed to identify failure rates in real circumstances, and not under experimental conditions such as those of clinical trials. Thus, the election of treatment was left to the criteria of the corresponding physician. The use of antibiotics was generalized and did not permit comparison of relapse rates between patients taking or not taking antibiotics. Moreover, the wide variety of broad spectrum antibiotics given, and the lack of random allocation to one or another, prevented any analysis of the effects of individual antibiotics on failure rate. Similarly, another Spanish survey in primary care showed that antibiotics were used in 89% of AECB, and second-line, broad-spectrum antibiotics were extensively prescribed irrespective of the severity of either the underlying disease or the exacerbation [13]. Therefore, the potential confounding effect of different antibiotics on outcomes can reasonably be ruled out. The effect of antibiotic treatment on relapse is controversial. BALL *et al.* [3] and DEWAN *et al.* [14] observed no effect of antibiotic treatment on the relapse rate of exacerbations; in contrast, baseline characteristics of the patients, similar to those found in the present study, such as the number of previous chest infections and history of cardiopulmonary disease, were the best predictors of return to the GP with a chest problem. However, when comparing first-line antibiotics, such as amoxicillin, with second-line agents, *i.e.* amoxicillin-clavulanate, cephalosporins, macrolides or quinolones, some studies showed a significant improvement in outcome for the latter group [4, 15]. Moreover, in a different setting such as in randomized, double-blind studies, different outcomes have been observed in high-risk patients, and results suggested quinolones could be first-choice therapy for more severe patients [16]. Similarly, pharmacoeconomic studies have shown that oral cephalosporines such as cefixime could be a cost-effective option for ambulatory treatment of AECB in mild-to-moderate patients [17].

The present study found an association between the number of visits to the GP the previous year for respiratory problems and increased risk of relapse; the risk of failure increased by 7.6% for every extra visit to the GP. The number of visits and the number of previous exacerbations were strongly correlated, suggesting that most visits to the GP were due to exacerbation symptoms. The number of visits was included in the model, since this should be more discriminative by showing the number of exacerbations severe enough to force the patient to seek medical attention. Recent examples suggest that the number of previous exacerbations may not be a reliable marker of severity; as an example, in a prospective study, SEEMUNGAL *et al.* [1] in a prospective study found that almost half of the exacerbations recorded on daily diary cards were not reported to their physicians. Similarly, their results showed frequent past exacerbations to be one of the factors most strongly associated with recurrent exacerbations [1]. In two other studies, the number of previous exacerbations was a risk factor for relapse after ambulatory treatment for an AECB [3, 14]. The high admission and relapse rates for previous visits were also a significant risk factor for predicting the probability of admission for decompensated lung disease in patients who attended an emergency unit [18]. These results, together with the present ones, suggest that there exists a subgroup of patients more prone to developing recurrent respiratory infections, even with the same degree of severity of the underlying disease.

The present study observed that the presence of coexisting diabetes or significant cardiac disease was associated with increased risk of relapse in univariate analysis. However, after multivariate analysis, only ischemic heart disease was still significant, with an increased risk of 63%. Similarly, other studies found coexistent cardiopulmonary disease to be a risk factor for referral to hospital after treatment for an acute exacerbation [3, 15], and cardiac comorbidity was found to be among the best predictors of mortality in a cohort of chronic obstructive pulmonary disease (COPD) patients discharged after an acute exacerbation [19]. In a previous retrospective study [20], the presence of ischemic heart disease or cardiac insufficiency were observed to be strongly correlated with an increased risk of hospital admission for decompensated COPD, with an OR of 1.97 (95% CI = 1.24 – 3.14). Conversely, ADAMS *et al.* [15] did not observe any association between comorbidity and outcome in a hospital-based population of severe COPD patients (29% with a forced expiratory volume in one second

(FEV1) <35% and 27% with oxygen therapy). These results suggest that cardiac comorbidity is a risk factor of poor outcome, particularly in mild-to-moderate patients; however, when the pulmonary disease is severe, the impairment in pulmonary function prevails over cardiac disease as a risk factor. Cardiac comorbidity may also provoke admission during exacerbations and even be a cause of death, particularly in elderly patients [20, 21].

Severity of the underlying disease is an important risk factor for relapse; patients with more severe dyspnoea at baseline were more at risk of returning to the GP with persistence or increase in symptoms. One possible explanation could be the demonstration that patients with more advanced bronchial disease are at increased risk of suffering exacerbations caused by bacteria more aggressive and resistant to antibiotics [22–24].

A limitation of the study is the subjective evaluation of severity based on the scale of baseline dyspnoea, instead of using objective measures of disability such as the FEV1 [25]. It must be considered that FEV1 is not readily available for most GPs in different countries. In Spain only 36% of GPs require pulmonary function tests in patients with obstructive lung disease [26, 27]. Similarly, in Canada, only 38% of GPs requested spirometry for chronic bronchitis patients [28]. Furthermore, quality of spirometry in the primary care setting is far from optimal and may yield conflicting results [29]. In this context, dyspnoea scales may be a reasonable and reliable measure of disability in patients with chronic obstructive lung disease [30]. It cannot be ruled out that some of the patients in the present study might have had asthma; however, a recent study in the UK observed that few asthmatics were mistakenly diagnosed as having COPD in primary care [31]. Based on the clinical characteristics of the present study's population, which are very similar to that of the aforementioned study [31], and having ever been diagnosed with asthma being an exclusion criterion, the authors do not believe that significant misdiagnosis of chronic bronchitis would have influenced the results.

Surprisingly, severity of the exacerbation did not influence outcome. However, severity of the disease was a determinant of outcome in placebo-controlled studies [9]. Since almost all patients in the present study were receiving broad-spectrum antibiotics, these results suggest that under broad-spectrum antimicrobial treatment, severity of symptoms of the exacerbation is no longer a risk factor for relapse. The present results, in a large cohort of patients, confirm the observations of previous studies [3, 14, 15] that also failed to find any significant effect of exacerbation severity on outcome in smaller populations. Nevertheless, another possible marker of severity of the exacerbation, such as sputum colour, has been suggested as a useful marker of bacterial infection and the need for antibiotic treatment [32]; the prognostic value of this readily-obtainable marker must be validated in future prospective studies.

The model developed here for prediction of relapse after ambulatory treatment of acute exacerbations of chronic bronchitis indicates that a patient with ischaemic heart disease, degree III dyspnoea (Mahler's scale [8]) and who visited the general practitioner three times in the last year for respiratory problems has a relapse probability of 32.4%, clearly higher than the mean 21% probability of the cohort. Considering the high prevalence of chronic bronchitis in the general population and the high number of medical consultations generated by this population, it is crucial to identify patients at risk for failure of treatment of exacerbations or at risk for repeated consultations for respiratory problems. Prospective studies, such as the present report, are useful for identifying and validating risk factors, some of which are already included in guidelines for management of patients with chronic bronchitis [33]. Patients exhibiting such factors should receive energetic treatment with broad-spectrum antibiotics, a short course of oral corticosteroids and should be closely followed-up in an attempt to avoid relapse which, in a significant number of cases, may lead to hospital admission or even be a cause of death.

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Appendix

Calculation of probability of relapse after ambulatory treatment of an exacerbation requires the steps following.

1. Compute the logit g(x) defined as:

$$g(x) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots\ldots b\beta_k x_k \quad (1)$$

where β_0 is the constant and $\beta_1 x_1$ is the estimated coefficient for the ith variable times the value of the ith variable, with i taking on the values from 1 to k, and k being the number of variables in the model. Number of exacerbations suffered the previous year and degree of dyspnoea are entered as numbers, while ischemic heart disease takes the values of 0 or 1, signifying the absence or presence, respectively.

2. Transform the logit into a probability through the following calculation:

$$P\ (\text{relapse}) = [e^{g(x)}/1 + e^{g(x)}] \quad (2)$$

For example, a patient with ischaemic heart disease and a degree of dyspnoea of III, who visited the general practitioner three times in the last year would have a probability of relapse after being treated for an acute exacerbation of:

$$\text{logit} = -2.2569 + 0.2722 \times 3 + 0.4898 \times 1 + 0.0726 \times 3$$

$$= -0.7327; e^{-0.7327}/1 + e^{-0.7327} = 0.3246$$

The probability of relapse is 32.4%. This probability is an estimate, or expectation, based on the relapse rate of a large group of similar patients and represents the proportion of patients expected to exhibit the outcome.