Patients hospitalized for COPD have a high prevalence of modifiable risk factors for exacerbation (EFRAM study)

J. Garcia-Aymerich*, E. Barreiro+, E. Farrero‡, R.M. Marrades§, J. Morera¶, J.M. Antó*,#, and the EFRAM investigators‡

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ABSTRACT: There is little information available concerning the extent to which chronic obstructive pulmonary disease (COPD) patients are satisfactorily managed, especially, regards factors supposedly related to COPD exacerbation. The present study assessed the prevalence rates of potentially modifiable risk factors of COPD exacerbation in patients hospitalized for this reason.

A systematic sample of one out of two patients admitted for COPD exacerbation, during 1 yr, in four tertiary hospitals in the Barcelona area, Spain, was performed. Patients answered a questionnaire and underwent anthropometric measurements, spirometric tests and arterial blood gas sampling. Prevalence rates and 95% confidence intervals (95% CI) for risk factors were obtained, and the generalized estimating equation (GEE) method was used to allow for patients to provide information on different admissions.

The study recruited 353 patients (29 female) with a total of 404 admissions age (mean±SD) 69±9, median forced expiratory volume in one second (FEV1) 31% of predicted and mean partial pressure of oxygen (P_{O_2}) 63±13 mmHg. Of these, 28% had not received an influenza vaccination; a high number (86%) did not attend rehabilitation programmes; 28% of patients with $P_{O_2} \leq 55$ mmHg were not using long-term oxygen therapy (LTOT); among LTOT users, 18% used it <15 h a day; 43% of the total failed in some of the essential inhaler manoeuvres; 26% were current smokers; 21% of noncurrent smokers were exposed to passive smoking at home; current occupational exposure was low (5%).

In summary, the authors found a moderate to high prevalence of potentially modifiable risk factors in a large representative sample of patients hospitalized for a chronic obstructive pulmonary disease exacerbation, suggesting unsatisfactory features in their management.
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*Respiratory and Environmental Health Research Unit, IMIM, Barcelona, +Dept of Pneumology, Hospital del Mar, Barcelona, ‡Dept of Pneumology, Ciutat Sanitària i Universitària de Bellvitge, L'Hospitalet de Llobregat, §Dept of Pneumology, Hospital Clinic i Provincial de Barcelona, Barcelona, ¶Dept of Pneumology, Hospital Germans Trias i Pujol, Badalona, #Dept of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain.

Correspondence: J.M. Antó, Respiratory and Environmental Health Research Unit, Institut Municipal d'Investigació Mèdica (IMIM) Universität Pompeii Fabro, Doctor Aiguader 80, E-08003-Barcelona, Catalonia, Spain. Fax: 34 32213237

Chronic obstructive pulmonary disease (COPD) is characterized by a chronic slowly progressive limitation of the airflow. As the damage is largely irreversible, the major goals of COPD management are to lessen airflow limitation, prevent and decrease symptoms, prevent and treat medical complications and improve daily living and quality of life [1]. The acute exacerbation of COPD is among the relevant events in the progression of the disease, and its occurrence has been related to the lower survival [2] and decrease in the quality of life [3] of COPD patients. Acute exacerbations are also an important cause of health expenditure, due to hospitalization, outpatient care and drug consumption [1].

Although respiratory infection is assumed to be the main risk factor for the exacerbation of COPD [4], other factors are also involved. Health education of patients, smoking cessation, pulmonary rehabilitation, good nutritional status, and early medical intervention are all considered helpful in preventing exacerbations [5]. Information concerning the extent to which COPD patients are satisfactorily managed

with regards these factors, although likely to show strong local variations, is relevant for the formulation of general COPD guidelines. However, the authors were only able to find one descriptive study [6] assessing the prevalence of factors such as medical treatment, long-term oxygen therapy (LTOT), influenza vaccination and pulmonary rehabilitation in patients hospitalized for COPD. This study included a small number of patients (n=80), recruited from one hospital only, and covered a period of no more than 8 weeks. The lack of knowledge about both the aetiological importance of some putative risk factors and the effectiveness of their modification, in terms of reducing COPD admissions, may have favoured an insufficient attention to this issue.

The EFRAM project was aimed at both the assessment of the prevalence of plausible risk factors of COPD exacerbation in a cross-sectional survey of patients hospitalized for this reason, and the identification of risk factors in a case-case design. The present study reports prevalence rates of potentially modifiable risk factors, using a large

sample of COPD patients admitted for an exacerbation of the disease, over a 1-yr period.

Methods

Design and subjects

A cross-sectional study, with systematic sampling of one out of two patients hospitalized or remaining in the emergency room for at least 18 h for an exacerbation of COPD, in four tertiary national health service hospitals in the Barcelona area over 1 yr (May 1 1997–April 30 1998) was performed.

The COPD diagnosis was obtained from the diagnostic section of the pneumology ward lists. The ward pneumologist's diagnosis was based on the anamnesis (current symptoms and medical history) and, when available, on the results of previous pulmonary function tests, following the European Respiratory Society (ERS) guidelines [1]. On admission, the first diagnosis of all the subjects was the exacerbation of COPD. The exclusion criteria were: 1) mentally unable to answer a questionnaire; 2) severe comorbidity; 3) transtracheal catheter; 4) living outside of the province of Barcelona. During recruitment, the patients excluded were replaced by those of the one in two system who had not been initially included. After the recruitment phase, three admissions were excluded because of a forced expiratory volume in one second ($FEV1$)/forced vital capacity ratio (FVC) >88%, 17 admissions for positive bronchodilator tests and one admission for a further diagnosis of pulmonary fibrosis. Nonresponders were not replaced and certain information was obtained from their medical records.

The protocol was approved by the Ethics Committees of the participating hospitals, and written informed consent was obtained from all the patients.

Measures

During hospitalization, patients were asked to complete a long questionnaire and anthropometric measurements were made. At least three months after hospitalization, and during a clinically stable period of COPD, patients performed a spirometric test and provided arterial blood to measure gas tensions. Neither spirometry or blood gases were repeated if the results were already available from the three months prior to hospitalization, during a period of clinical stability.

Information about potentially modifiable risk factors of COPD exacerbation was obtained by an extensive bibliographic search (Medline and The Cochrane Library) for "COPD" and "exacerbation/admission/hospitalization". Certain known risk factors for the exacerbation of COPD were found: no influenza vaccination [7] and high air pollution exposure [8]. In addition, other factors were found, related to the poor progress of the disease, that could be considered potential risk factors for exacerbation: no respiratory rehabilitation [9], underprescription of LTOT and noncompliance with it [10, 11], current [12] and passive [13] smoking and occupational exposure [14]. Other potentially relevant factors as suggested by members of the study group were: poor inhaler manoeuvres, no

pneumococcal vaccination, consumption of alcohol and sedatives, and no physical activity.

Sociodemographic data, and a list of 11 chronic conditions, were obtained from questions used in health surveys in Barcelona [15]. Socioeconomic status was assigned according to occupation, using an adapted version of the British Registrar General's Social Classes [16]. Dyspnoea before exacerbation was assessed retrospectively with the Borg scale [17]. Factors related to health services were as follows: characteristics and content of visits to the physician monitoring the disease, number of hospitalizations and emergency and doctor's visits during the previous year, current pharmacological treatment, LTOT, influenza and pneumococcal vaccination and pulmonary rehabilitation. For most of these, an *ad hoc* questionnaire was developed which was piloted for understanding and feasibility. Influenza and pneumococcal vaccinations were self-reported by the patient and taken from the vaccination card, whenever available. Rehabilitation was defined as when the patient reported doing rehabilitation exercises or respiratory gymnastics, including blowing up balloons or balls. Underprescription of LTOT was defined as when the patient had PO_2 <55 mmHg and did not use LTOT. Noncompliance with LTOT was defined as when the patient reported using it <15 h a day. Other exposures included: active and passive smoking [18], occupational pollution exposure [18], alcohol consumption [15], sedative consumption and physical exercise. Current smokers were defined as those who had smoked during the month prior to hospitalization. Passive smoking was defined as when "somebody" smoked regularly in the patient's house. Occupational exposure was defined as a positive answer to the question, "Do you work exposed to vapours, gas, dust or fumes?". No physical activity was defined as when the patient did not walk, climb stairs, do any other physical exercise or attend respiratory rehabilitation. Inhaler compliance was measured with inhaler-specific checklists [19], and the three items considered essential for metered dose inhalers (MDI) were: "shaking before use", "inhaling slowly while simultaneously activating the canister" and "inhaling slowly throughout discharge" [19]. Physical examination included weight, height and tricipital skin-fold thickness. The clinical register of the hospital revealed whether or not this was the first time the patient was admitted for COPD.

Spirometry and the bronchodilator test were performed using standard techniques [20]. Reference $FEV1$ values were obtained from selected volunteers from the Barcelona area [21]. The severity of COPD was staged according to American Thoracic Society guidelines [22], selected *a posteriori* because ERS cut-off points did not discriminate in the present study sample. Blood gas tensions were measured breathing room air. Cut-off points for PO_2 were taken from indications for LTOT administration of COPD guidelines [1, 22].

Statistical analysis

Sample size estimations suggested that 452 episodes would have to be recruited to obtain prevalence rates of 50% with a precision of ±5%, accepting an alpha risk of 0.05 for a two-sided test, and anticipating a nonresponses rate of 15%. Bearing in mind the number of COPD

discharges in the four hospitals in 1996 (n~1400), systematic sampling of one out of two COPD admissions was decided upon. Patients were allowed to enter the study as many times as they were hospitalized during the study period.

A comparison of responses and nonresponses was made with an unpaired t-test (for quantitative variables of normal distribution), Wilcoxon test (for quantitative variables of non-normal distribution) or Chi-squared (for qualitative variables). In order to allow the patients with more than one admission to provide information on the different admissions, the generalized estimating equation (GEE) method, with an unstructured correlation matrix to allow for within-individual correlation, was used [23]. Moreover, this method provides individual-based proportions. a more interpretable result than episode-based proportions. Proportions and 95% confidence intervals (95% CI) of modifiable known or potential risk factors of exacerbation were calculated from logistic regression estimates, adjusting for sex, age, marital status and level of education. A comparison between categories of variables in the logistic model was carried out with the Wald test. The analysis was performed with Stata, release 5.0 (StataCorp, College Station, TX, USA).

Results

Table 1, shows the demographic and clinical characteristics of the study sample. A total of 492 eligible episodes were approached, from which 404 (353 patients) accepted to participate. The reasons for nonresponse (n=88 admissions (78 patients), 18% of total) were: 79 refusals, two discharges before the interview and seven deaths. Nonresponders (table 1) did not differ in terms of the number of admissions, sex, age, length of hospital stay and percentage of predicted FEV1, from responders, although the proportion that were married was lower and they had less comorbidity. Regarding risk factors, there was no difference in current smoking, alcohol intake or influenza vaccination between responders and nonresponders, but the nonresponders used more LTOT (51% versus 33%, p=0.004). For 63 admissions (61 patients) spirometric data was not available (because the patients had died, dropped out, could not perform the test or were clinically unstable all the time). These patients had less comorbidity (79% versus 92%, p=0.004) than patients who had performed spirometric tests, but no difference was found in the remaining variables.

Most of the risk factors showed moderate to high prevalence (table 2). The most frequent risk factors were no rehabilitation (86%) and failures with the MDI manoeuvre (43%). Current occupational exposure (5%) and noncompliance with LTOT (18%) were less common. The frequency of current smokers was lower in females when compared to males (10% versus 27%, p=0.038). Stratifying age in tertiles (<65 yrs; 65–73 yrs; >73 yrs), the youngest group made less mistakes with inhaler manoeuvres (32% versus 48% and 48%, p=0.018) and a trend was observed with regards active smoking (40%, 29% and 11%, p<0.0005). After adjusting for sex and age, the only difference between married and unmarried (single, widowed or divorced) subjects, was in terms of inhaler manoeuvres in married subjects (37% of some mistake versus 57%, p=0.002). The same was true for patients with at least primary education with respect to those who had received less than primary education (32% versus 51%, p<0.0005). No difference was found in the prevalence of risk factors between subjects who belonged to high (I-III) or low (IV-V) socioeconomic status, or between patients hospitalized for the first time for COPD

Table 1. – Characteristics of patients hospitalized by chronic obstructive pulmonary disease (COPD) exacerbation in the Barcelona area during May 1997–April 1998

	Responders			Nonresponders	p-value*
	Males	Females	Total	Total	
Subjects n	324	29	353	78	
Number of admissions					
1	284 (88)	26 (90)	311 (88)	70 (90)	0.593
2	34 (10)	3 (10)	37 (10)	6 (8)	–
>2	6 (2)	–	6 (2)	2 (2)	–
Males			324 (92)	71 (91)	0.826
Age yrs	69±9	72±10	69±9	71±8	0.067
Married	250 (77)	8 (28)	258 (73)	42 (54)	0.001
Current workers	22 (7)	2 (7)	24 (7)	–	–
Less than primary education	187 (58)	20 (69)	207 (58)	–	–
Socioeconomic status IV or V	232 (72)	23 (79)	255 (72)	–	–
Admissions n	372	32	404	88	
Length of hospital stay	9 (6–14)	11 (6–19)	9 (6–14)	8 (5–15)	0.131
At least one coexisting chronic condition[+]	331 (89)	31 (97)	362 (90)	60 (75)	0.000
Percentage of predicted FEV1	30 (23–39)	43 (33–46)	31 (23–41)	31 (23–41)	0.920
P_{O_2} mmHg	63±13	60±14	63±13	–	–
Dyspnoea score	3.7±2.2	3.2±2.3	3.7±2.2	–	–
Hospitalizations for COPD[#]	1.9±2.4	2.1±3.2	1.9±2.5	–	–
Body mass index kg·m⁻²	25.6±4.6	30.6±8.0	26.0±5.1	–	–

Data are presented as n (%), mean±SD or median (interquartile range). *: comparison between responders and nonresponders; [+]: 8 missing values in nonresponders; [#]: data includes hospitalizations in the last year. FEV1: forced expiratory volume in one second; P_{O_2}: partial pressure of oxygen. T-test for age; Wilcoxon test for length of hospital stay and FEV1; and Chi-squared for number of admissions, sex, marital status and coexisting chronic conditions.

and those with previous admissions for COPD, or between admissions in winter (October-March) and summer (April-September). After adjusting for sex, age, marital status and level of education, current smoking was less frequent in the more severe group of patients (table 2). Apart from that, no other differences were found between the different groups of severity or the group with no spirometric readings. With respect to the prevalence of other potential risk factors of exacerbation, 97% of individuals had not received pneumococcal vaccination, 16% reported no physical activity, 32% and 15% respectively consumed alcohol and sedatives in the previous month, after adjusting for sex, age, marital status and level of education.

Other information regarding the patient's attitude and the doctor's advice was obtained. Ninety-two per cent of current smokers had at some time tried to stop or cut down. Although 95% of current smokers had been advised in the past year not to smoke by their principal physician only 36% reported receiving advice about the best way to stop smoking. With respect to the methods that could be employed, only 17% received information about nicotine replacement therapy, 13% about smokers groups and 20% about specialized services. Only half of the patients reported that their physicians had recommended that they should not be exposed to smoking at home. Of the 28% of subjects with underprescription of LTOT, 21 subjects (88%) had previously been admitted for COPD, and 10 (42%) currently smoked. MDI was the most frequently used bronchodilator device in the study sample (88% *versus* 1% Accuhaler® and 12% Turbohaler®). Although 85% of subjects reported having been taught inhaler manoeuvres at their first visit to the physician, and 80% rechecked at each of the following visits, 43% of them had failed to adequately perform some of the essential MDI manoeuvres, while only 16% failed to adequately perform some of the essential Turbuhaler® manoeuvres.

Discussion

A high prevalence of several modifiable risk factors was found, such as "no rehabilitation" and poor inhaler manoeuvres, in patients hospitalized for COPD exacerbation. Other factors, such as no influenza vaccination, underprescription of LTOT and smoking, showed a moderate level of prevalence, likewise important for their potential harmful effects.

The overall influenza vaccination rate for the group of exacerbated COPD patients was 72%, higher than the 40% found by POOLE *et al.* [6] in a similar group of patients, it was also similar to the 70% found in other population-based studies of chronic respiratory patients [7]. Many guidelines for COPD recommend influenza vaccination, as it protects against hospitalization and death in chronic respiratory patients [7].

The number of patients found to be attending pulmonary rehabilitation programmes was 14%, a level which falls between the 5–8% found in Switzerland [24] and the 24% in New Zealand [6]. If the criteria of the COPD guidelines were applied to recommend rehabilitation [1, 22] to the patients in the study, >90% should have been included in a rehabilitation programme. Although the direct effect of respiratory rehabilitation on the use of the health services remains controversial, it has been found to be effective in reducing dyspnoea and improving the quality of life [9]. The low rate of rehabilitation is due to the lack of provision in the study hospitals during the recruitment year. Currently, only one of four hospitals is systematically offering a short programme of muscular training for COPD patients after the admission. In the current context of cost-containment, the lack of evidence with regards the effectiveness of rehabilitation, until recently [9], and the limited evidence on its cost-effectiveness for COPD patients [25], is in favour of the argument that rehabilitation programmes for COPD are not offered frequently enough.

The prevalence of current smoking was 26%, slightly lower than the 33% [6] or 34% [26] reported by other studies on COPD patients hospitalized for exacerbation, but it is still a high proportion considering the consequences. Stopping smoking is the main treatment for COPD [1, 22], and the patients that do not succeed will see their FEV_1 decreasing at a faster rate [12]. In addition, it was found that 21% of noncurrent smokers were exposed to passive smoking at home, which is likely to be harmful, although the effect of passive smoking on patients suffering from COPD has not been assessed [13]. Overall, the authors found that little specific advice about methods for quitting active or avoiding passive smoking is given by the physician, something which must be addressed, considering that it is currently being recommended for all health

Table 2. – Prevalence of risk factors, by severity of the disease (American Thoracic Society classified stages), adjusted for sex, age, marital status and level of education

	Total (353/404)*	$FEV_1 \geq 50\%$ (41/42)	$FEV_1=35-49\%$ (73/81)	$FEV_1 <35$ (178/218)	Missing FEV_1 (61/63)
No influenza vaccination	28 (24–33)	28 (16–43)	26 (17–36)	29 (23–35)	28 (18–40)
No rehabilitation in the last year	86 (82–89)	94 (83–98)	90 (81–95)	84 (78–88)	86 (75–93)
No LTOT when $PO_2 \leq 55$ mmHg	28 (20–39)		50 (17–83)	26 (17–38)	
LTOT <15 h·day^{-1}	18 (13–25)	34 (11–67)	23 (9–48)	13 (8–21)	35 (17–60)
Fail essential inhaler manoeuvres (MDI)	43 (38–48)	48 (30–66)	36 (25–48)	43 (36–50)	47 (33–61)
Current smoking	26 (22–31)	33 (20–50)	31 (22–43)	17 (13–23)+	30 (19–43)
Passive smoking in noncurrent smokers†	21 (17–26)	26 (13–46)	19 (11–32)	19 (14–26)	25 (14–40)
Current occupational pollution exposure	5 (3–8)	2 (0–12)	1 (0–4)	0 (0–2)	1 (0–6)

Data presented as prevalence (95% confidence interval). *: Number of individuals/admissions; †: 90% of whom are exsmokers; +: p=0.004 in comparison to the groups of moderate and mild disease; -: not possible to calculate due to small sample size; FEV_1: forced expiratory volume in one second; LTOT: long-term oxygen therapy; MDI: metered dose inhalers.

professionals to give advice on nicotine replacement therapy to all smokers at every opportunity [27].

The indications for LTOT for COPD patients are well established [1, 22]. Patients who need LTOT but do not use it will have a poorer survival rate than those correctly treated [10, 11]. In Catalunya, a great effort has been devoted to improve LTOT prescription [28], but yet a moderate rate of underprescription was found in this study (28%), which shows that there is a need to improve hospital and outpatient management schemes. In the present sample, LTOT noncompliance was found to be ~20%, lower than the 44% [29] or 55% [30] reported by other studies that measured compliance from the concentrator counter. The most likely explanation for the difference is that self-reported habits in this study could result in an increased compliance rate being recorded.

Of the patients, 43% failed in some of the essential MDI manoeuvres, this was lower than the 76% found by VAN DER PALEN et al. [19] in COPD patients attending an outpatient department. Other studies found a high prevalence of noncompliance with MDI in COPD [31] or asthmatic [32] patients, and even in medical personnel [33]. This, together with the fact that a high proportion of the patients in the present study reported having been taught the inhaler manoeuvre (and rechecked), and that there are less mistakes made with dry powder devices than with MDI, could suggest that the problem is inherent to the MDI, rather than related to the patients or physicians. Other bronchodilator devices are more expensive, but their prescription should be considered if the correct deposition of the bronchodilator in the lungs is to be ensured.

Although current exposure to occupational pollution was low (5%), partly due to the low numbers currently working (7% of total), whether the patients were taking protective measures in the workplace would need to be assessed, as per the ERS guidelines recommendations [1], and the measures of social protection available also need to be considered.

One of the limitations of the present study is that the inclusion of the various risk factors of COPD exacerbation was not based on a systematic critical appraisal of the literature. For this reason, a substantial part of the discussion provides a narrative review of the available literature. Although the authors see their approach as appropriate in the context of the current knowledge, it is clear that more research is needed concerning the nature and importance of the determinants of COPD exacerbations. The present study was hospital-based both because its feasibility and the economic importance of COPD admissions. However, its results should be interpreted with caution and not generalized to the whole COPD population. A risk factor of hospitalization in exacerbated COPD patients will always be more prevalent in a hospital based sample than in a community-based sample the difference between both prevalences being a function of the magnitude of the relative risk. Although further studies in community-based samples of COPD patients are needed, the results strongly suggest that COPD patients in general are not sufficiently well managed and that there is a large potential for improvement.

A degree of nonresponse (selection) bias is probably present, although the participation rate was 82%, higher than in other studies on hospitalized COPD patients requested to answer a questionnaire [6, 34]. The lower prevalence of coexisting chronic conditions in nonresponders could be explained by the fact that there was no data in the medical record about the milder diseases that were asked about in the questionnaire (e.g. rheumatism or headaches). The higher prevalence of LTOT amongst the nonresponders may suggest that these patients have a more severe disease, although no differences in FEV1 were found. The authors opinion is that nonresponse has not led to a biased prevalence. The lack of lung function tests for some patients could be seen as a problem of misclassification, as some non-COPD subjects could have been included. However, only 5.5% of all episodes with spirometry performed were excluded due to either a FEV1/FVC ratio >88% or a positive bronchodilator test. If this 5.5% level was applied to episodes without spirometric values (n=62), only three of them would have been excluded. Moreover, the comparison between patients with performed tests and those without, only showed differences in the proportion of comorbidities, and no other differences were found in sociodemographic or clinical variables or in the prevalence of risk factors. In the authors view, if there is some misclassification, it has very little impact on the prevalence rates.

It may be argued that the present results are merely a reflection of local practices and therefore, cannot be generalized. However, as shown in the discussion, a moderate to high prevalence for most of the risk factors considered has been observed in many different areas. Even if some of the observed results are only local, the description and understanding of local variations in other fields of healthcare have proved to be a very successful research approach [35].

To conclude, a moderate to high prevalence of potentially modifiable risk factors in a large representative sample of patients hospitalized for a COPD exacerbation was found, suggesting unsatisfactory features in their management. For those factors with well established relevance in chronic obstructive pulmonary disease exacerbation, more effort in monitoring and improving patterns of care is needed. For some of the factors suspected to be relevant for chronic obstructive pulmonary disease exacerbation, the high prevalence rates reported in the study reveal the need to investigate their true impact on its exacerbation.

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