

Relationships Between Treatment Outcome and Severity of COPD and Frequency of Exacerbation Episodes in Patients With COPD

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Abstract

This retrospective study on patients with acute exacerbations of COPD admitted to the emergency service of a research hospital was designed to assess the factors that affect treatment outcome in such patients. The records of 81 patients who were hospitalized in their previous exacerbation in our hospital and who were admitted to the emergency service with yet another exacerbation were reviewed. A total of 91 instances of exacerbations during a six month period were classified into two groups according to the time elapsed between the two episodes. Group I (successful treatment, n=73) included the patients admitted with a new exacerbation after at least 30 days of discharge, and group II (treatment failure, n=18) those admitted within the first 30 days after discharge.

Group II subjects had severe COPD, a longer smoking history ($p=0.008$), more frequent exacerbations ($p=0.004$) and hospitalizations ($p=0.003$) in the previous year. Long term pharmacological therapy, use of long term oxygen therapy, vaccination status, choice of antibiotics and use of steroids in the previous exacerbation did not differ between the groups. The results of our study demonstrated that treatment failure is more likely to occur in patients who had severe COPD and a higher frequency of exacerbations in the previous year. Therapeutic maneuvers did not appear to affect treatment outcome.

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Keywords: acute exacerbation, COPD, treatment outcome

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by progressive and mostly irreversible airflow limitation usually associated with an abnormal inflammatory response of the lungs to noxious particles or gases (1). It is a major cause of chronic morbidity and mortality throughout the world and is currently the fourth leading cause of death (2). The acute exacerbation of COPD, defined as an acute episodic deterioration superimposed on stable COPD, is the main cause of presentation of patients with COPD to physicians or to hospitals (3). Frequent hospital admissions and absenteeism from work results in a significant financial cost and socioeconomic burden to society (4). Acute exacerbations of COPD are also among the relevant events in the progression of the disease and have been related to a lower survival (5) as well as to a decrease in the quality of life (6,7). Treatment that improves quality of life and limits hospital admissions and relapses constitutes an important element in reducing the impact of the disease on the patient's life and in tapering treatment costs.

The goals of the treatment in acute exacerbation of COPD are the prompt resolution of symptoms and minimization of failure

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Table 1. Demographic and clinical characteristics of patients in the two groups

Variables	Group I (n=73)	Group II (n=18)	p
Age (years)	65.4±9.1	62.5±8.4	NS
Sex, male	73.9% (n=54)	94.4% (n=17)	NS
Smoking history (pack-years)	41.2±40.5	65.8±35.3	0.008*
Non smokers	28.8% (n=21)	5.6% (n=1)	NS
Active smokers	46.6% (n=34)	22.2% (n=4)	NS
Ex smokers	24.6% (n=18)	72.2% (n=13)	0.0*
Give up smoking days	1407.4±2329.2	2566.1±3002.6	NS
History of alcoholism	20.5% (n=15)	5.6% (n=1)	NS
Previous pulmonary disease			
Pneumonia	5.4% (n=4)	-	NS
Sinusitis	10.9% (n=8)	-	NS
Comorbid medical conditions			
<i>Cor pulmonale</i>	46.6% (n=34)	61.1% (n=11)	NS
Ischaemic heart disease	26% (n=19)	27.8% (n=5)	NS
Congestive heart failure	6.8% (n=5)	11.1% (n=2)	NS
Hypertension	35.6% (n=26)	22.2% (n=4)	NS
Diabetes mellitus	9.6% (n=7)	-	NS

NS: Not significant.
*statistically significant.

rate. Despite adequate therapy, the outcome may not be satisfactory and re-admissions may occur. Factors such as severity of COPD, age, co-morbid diseases, socioeconomic status, quality of life, usage of long term oxygen therapy, antibiotic choice and other therapeutic modalities have been shown to affect the treatment outcome in COPD acute exacerbations (6-10). In this study, we aimed to determine the causes of early re-admissions and factors affecting the treatment outcome after an acute exacerbation of COPD.

Materials and Methods

The study was conducted in the Atatürk Chest Diseases and Thoracic Surgery Research Hospital emergency service between July and December 2002. Eighty-one COPD patients (61 male, 20 female) who were hospitalized in the previous exacerbation and admitted again with another exacerbation were included in the study. During this 6 months period a total of 91 exacerbations (8 patients had 2 exacerbation, 1 patient had 3 exacerbation) occurred. We retrospectively reviewed the hospital files of every previous exacerbation individually.

The diagnosis of COPD and acute exacerbation was made according to the criteria of the European Respiratory Society (3). Acute exacerbation is defined as the presence of any combination of the three following symptoms lasting more than 48 hours: 1) Increased cough and sputum volume 2) Increased sputum purulence 3) Increased dyspnea. Patients were excluded from the study if their previous exacerbation was treated on an ambulatory basis, if they were hospitalized in another hospital and if they had exacerbations due to secondary causes such as pneumonia, pneumothorax, pulmonary embolism, congestive heart failure, etc. The diagnoses of active tuberculosis, bronchiectasis and lung

cancer were also exclusion criteria.

The exacerbations were classified into two groups according to the time elapsed between the two exacerbations. Group I (successful treatment, n=73) included patients admitted with another exacerbation after an elapse of more than 30 days after discharge from the previous exacerbation, group II (treatment failure, n=18) those admitted within the 30 days following discharge.

Demographic data including age and sex, history of smoking and alcoholism, and history of previous pulmonary diseases, sinusitis and co-morbid medical conditions were obtained at each exacerbation. Duration of COPD, number of exacerbations and hospitalizations in the previous year, vaccination status, use of long term oxygen therapy (LTOT), use of nebulisers, and long term pharmacological therapy, as well as lung function data based on pulmonary function tests and arterial blood gas analysis during the stable stage of the disease were also recorded. The choice of antibiotics, their way of administration, dose, duration and concomitant use of systemic steroids in the previous exacerbation were noted.

Statistical analysis was carried out using SPSS package program version 10.0. Demographic and baseline clinical characteristics were expressed as means and standard deviations (\pm SD). The Mann-Whitney U test was used for specific comparisons. Categorical variables were compared by means of the χ^2 test. The correlation between clinical variables was evaluated using the Pearson's correlation coefficient. Any p value <0.05 was considered significant.

Results

Seventy three patients (54 males, 19 females) constituted group I, and 18 patients (17 males, 1 female) constituted group II. Mean duration between the two exacerbations was

Table 2. Duration of COPD, number of exacerbations and hospitalizations in the previous year, vaccination status, use of nebulisers, and long term pharmacological therapy of the patients

Variables	Group I	Group II	p
Duration of COPD (years)	10.8±8.6	11.4±7.4	NS
No of exacerbations	3.7±2.03	5.6±3.03	0.004*
No of hospitalizations	1.8±1.3	3.1±1.6	0.003*
Vaccination status (influenza)	23.3%	16.7%	NS
Use of nebulisers	60.3%	61.1%	NS
Long term pharmacological therapy			
Theophylline	76.7%	100%	0.02*
Ipratropium	15.1%	22.2%	NS
Ipratropium+salbutamol	61.6%	77.8%	NS
Short-acting β -agonist, inhaled	39.7%	50%	NS
Long-acting β -agonist	30.1%	50%	NS
Steroids, inhaled	38.4%	61.1%	NS
Steroids, systemic	2.7%	5.6%	NS

NS: Not significant.

* statistically significant.

Table 3. Frequency of indication for LTOT, home oxygen use and mean duration between the last two exacerbations in the two groups

Variables	Group I	Group II	p
Patients (n)	73	18	
LTOT indication	33 (45.2%)	12 (66.6%)	0.103
Home oxygen	20 (60.6%)	4 (33.3%)	0.1
Duration between the last two exacerbations (days)	81.7±57.4 (range; 35-289)	12±3.7 (range; 7-16)	0.002*

LTOT: Long term oxygen therapy

*statistically significant

150.2±132.1 days (range; 35-710) in group I and 15.7±7.1 days (range; 6-30) in group II. Treatment failure rate was 19.8% (18/91). Demographic and clinical characteristics of the patients in the two groups are summarized in Table 1. The groups did not differ by age, sex, history of alcoholism, history of previous pulmonary disease, sinusitis and co-morbid medical conditions.

Group II patients were heavier smokers than group I patients ($p=0.008$). Most of the group II subjects (72.2%) were ex-smokers ($p=0.0$). Twenty one patients (15 female, 6 male) in group I and one female patient in group II were non smokers. A total of 16 patients (16/22, 72.7%) were female among the non smokers. Four of the females were recorded as passive smokers.

Duration of COPD, number of exacerbations and hospitalizations in the previous year, vaccination status, use of nebulisers, and long term pharmacological therapy of the patients are summarized in Table 2. Duration of COPD did not differ between groups, but group II subjects had more frequent exacerbations ($p=0.004$) and hospitalizations ($p=0.003$) in the previous year. Vaccination ratio for influenza was low but similar in both groups. Use of nebulisers was also similar in the two groups. Long term pharmacological therapy, except for the significantly high use of theophyllines in group II ($p=0.02$), were similar in the two groups.

An indication for LTOT was established in 33 patients (45.2%; 31 with $\text{PaO}_2 \leq 55$ mmHg and/or $\text{SaO}_2 \leq 88\%$ and 2 with cor pulmonale and PaO_2 of 55-59 mmHg) in group I and in 12 patients (66.6%, all had a $\text{PaO}_2 \leq 55$ mmHg and/or $\text{SaO}_2 \leq 88\%$) in group II. Indication for LTOT was higher in group II, but the difference was not statistically significant. Twenty patients (60.6%) in group I, and 4 patients (33.3%) in group II had home oxygen. The difference between the two groups was not significant. In patients who did not have access to oxygen sources at home, this was due mainly to their low socioeconomic status. The time period between the last two exacerbations was significantly longer in group I patients who had home oxygen than the patients who had home oxygen in group II ($p=0.002$). The ratio of indication for LTOT, frequency of home oxygen use in the two groups and the duration between the last two exacerbations are listed in Table 3.

Results of pulmonary function tests and arterial blood gas analysis in the stable disease period are summarized in Table 4. Mean values for FEV_1 in percentages were not significantly different between the two groups, but the mean of FEV_1 in liters was lower than 1 liter in group II. The major parameters of airway obstruction, FEV_1/FVC and FEF_{25-75} were significantly low ($p=0.034$, $p=0.004$) in group II. Group II subjects were more hypoxemic ($p=0.031$) and hypercapnic

Variables	Group I	Group II	p
FEV ₁ (%)	43.2±18.2	34.4±16.5	NS
FEV ₁ (lt)	1.2±0.5	0.9±0.5	0.043*
FVC (%)	57.4±21.7	53.7±19.1	NS
FEV ₁ /FVC	60.8±17.7	49.1±14.1	0.034*
FEF ₂₅₋₇₅ (%)	23.2±13.7	13.0±10.9	0.004*
PaO ₂ (mm Hg)	57.8±12.5	50.9±10.5	0.031*
PaCO ₂ (mm Hg)	44.1±9.5	50.2±9.5	0.021*
SaO ₂ (%)	88.0±6.5	82.3±9.1	0.012*

NS: Not significant.
* statistically significant.

Variables	Group I	Group II	p
Hospitalisation days	18.7±8.4	22.0±6.3	NS
Without antibiotics	8.2%	5.6%	NS
SAM or CAM	73.9%	72.2%	NS
Other antibiotics*	17.9%	22.2%	NS
Route of administration			
Orally	53.7%	52.9%	NS
Parenterally	43.3%	35.3%	NS
Consecutively	3.0%	11.8%	NS
Duration of antibiotic use (days)	12.4±3.3	12.6±2.6	NS
Concomitant use of systemic steroids	41.1%	61.1%	NS
Duration of systemic steroids (days)	12.6±7.3	11.4±3.1	NS

NS: Not significant.
SAM: Sulbactam ampicillin, CAM: Clavulanate-amoxicillin.
*Ceftriaxon, claritromycin, ciprofloxacin, cefuroxime axetil, levofloxacin, penicilline.

(p=0.021) than group I subjects. Based on these findings we conclude that group II subjects had more severe COPD than group I subjects. We found a negative correlation between oxygen saturation and number of exacerbations in the previous year (r=-0.25, p=0.019). Partial oxygen pressure (r=-0.34, p=0.002), oxygen saturation (r=-0.38, p=0.0) and partial carbon dioxide pressure (r=0.26, p=0.019) were also correlated with the number of hospitalizations in the previous year.

The hospitalization days, choice of antibiotic, way of administration, duration and concomitant usage of systemic steroids are summarized in Table 5. The hospitalization days were similar between the two groups, being 18.7±8.4 days for group I and 22.05±8.3 days for group II. In group I, 91.8%, in group II, 94.4% of the patients were treated with antibiotics. Sulbactam-ampicillin or clavulanic acid-amoxicillin were the most frequently used antibiotics with a ratio of 73.9% and 72.2% in group I and II respectively. Route of administration and duration were also similar. Concomitant steroid therapy was relatively high in group II, but it did not reach statistical significance. Duration of steroid therapy was also similar.

Discussion

COPD is a disease characterized by chronic and mostly irreversible airflow limitation and is associated with acute exacerbations of symptoms. It has been estimated that the average COPD patient experiences about 1 to 4 acute exacerbations per year and exacerbations are the most frequent causes of hospital admissions and death among patients with COPD (5). Furthermore, health care utilization is significantly increased and the quality of life of the individual is considerably reduced during exacerbations (4,6,7). The relapse rates after an acute exacerbation were found unexpectedly high ranging from 15% to 25% in observational studies (11-13) and 19.8% in our study. Since relapse after initial treatment for acute exacerbation may lead to prolonged disability, need for a new course of antibiotics, and an emergency visit or even hospitalization, it is crucial to identify patients most at risk of relapse and treat them more aggressively (14).

The outcome of any given treatment generally depends on the severity of illness, host factors and the given treatment (11,15). Severity of COPD, age, co-morbid diseases, socioeconomic status, quality of life, use of long term oxygen

therapy, antibiotic choice and other therapeutic modalities were found to be associated with treatment outcome in COPD acute exacerbations (6-10). The results of our study confirmed that the treatment outcome is poor and more likely to fail in patients who had severe COPD and a higher frequency of exacerbations. Age, co-morbidities, long term pharmacological therapy, LTOT, vaccination status, antibiotic choice and concomitant use of steroids during exacerbation did not affect the treatment outcome.

Increasing age is thought to be a risk factor for frequent exacerbations (14). In our study, mean ages of group I and II were 65.4 ± 9.1 and 62.5 ± 8.4 years respectively and may be because of the limited study sample size, were not found to differ significantly in the two groups.

Patients in group II in our sample were heavier smokers than group I patients, indicating that smoking is an important risk factor in COPD and in frequency of acute episodes in these patients. The frequency of non smokers was higher in female patients as compared to males. Four of the females were recorded as passive smokers. However, biomass exposure could be the reason for development of COPD in the others. It is important to mention that in Turkey a high proportion of the females living in villages are at a serious risk of biomass exposures, which is also a well known risk factor of COPD. Environmental factors such as air pollution, occupational exposures and low socioeconomic status could be possible risk factors also for the non smoker male patients.

It has been observed that the presence of coexisting ischemic heart disease is associated with increased risk of relapse (15). Similarly coexisting cardiopulmonary disease was found to be a risk factor for referral to hospital after treatment for an acute exacerbation (12,13). In a previous retrospective study, it was observed that the presence of ischemic heart disease or cardiac insufficiency correlated strongly with an increased risk of hospital admission for decompensated COPD (16). Conversely, as in our study, Dewan et al showed that the presence of co-morbidities did not affect the treatment outcome (11).

In accordance with our study, it was demonstrated that patients with impaired lung functions experience more frequent exacerbations (11,17,18) and a high number of previous exacerbations was found to be one of the predictors of the risk for frequent exacerbations in the future (17,33). Miravittles et al showed that baseline characteristics of the patients such as degree of dyspnea, coexisting ischemic heart disease and number of previous visits for respiratory problems are strongly associated with increased risk of relapse after ambulatory treatment of acute exacerbations of COPD (16). In the study by Lau et al, hospital admission for COPD exacerbation in the previous year, hospital stay longer than 5 days, nursing home residency, dependency in self-care activities, right heart strain pattern on electrocardiogram, using high dose inhaler corticosteroid and actual bicarbonate level >25 mmol/L were independently associated with shorter time to re-admission (8). Duration of COPD for longer than 10 years and increased severity of chronic

bronchitis have also been shown to be risk factors for poor outcome (19). In our study the duration of COPD was not significantly different in the two groups.

The most common causes of an exacerbation are infections of the tracheobronchial tree and air pollution, but the precipitating factor cannot be identified in approximately one third of severe exacerbations (1). The role of bacterial infections, once believed to be the main cause of COPD exacerbations is controversial for two main reasons. First, patients with COPD are often chronically colonized with bacteria even during the stable periods and second, many exacerbations are due to nonbacterial causes (31,32). For this reason, the role of antimicrobial agents in the treatment of acute exacerbations of COPD is also controversial. Placebo-controlled studies involving small numbers of patients have provided conflicting evidence of the efficacy of antibiotics in acute exacerbations of COPD (20). A meta-analysis of nine placebo-controlled trials concluded that, overall, there was a small but significant benefit from antibiotic treatment of acute exacerbations of COPD in terms of overall recovery and change in peak flow (21).

Antimicrobial therapy is indicated in patients in whom there is an increase in breathlessness accompanied by an increase in sputum volume and purulence (15,32). The choice of agents should reflect local patterns of antibiotic sensitivity among *S. pneumoniae*, *H. influenzae*, *M. Catarrhalis*. The effect of antibiotic therapy on relapse is also controversial. Comparing first-line antibiotics, such as amoxicillin, tetracycline, erythromycin, trimethoprim-sulphamethoxazole with second-line antibiotics, such as amoxicillin-clavulanate, ampicillin-sulbactam, cephalosporins, macrolides or quinolones, some studies showed a significant improvement in outcome for the latter group (12,22). Moreover, different outcomes have been observed in severe COPD patients suggesting quinolones to be first-choice therapy (19). Dever et al, believe that amoxicillin-clavulanate and fluoroquinolones should generally be reserved for patients with more severe disease (31). One possible explanation for choosing broad-spectrum antibiotics in exacerbations of severe COPD patients could be the demonstration of bacteria which are more aggressive and which show a greater resistant to antibiotics (23).

Ball et al (13) and Dewan et al (11) observed no effect of antibiotic therapy on the relapse rate of exacerbations. The majority of patients in both groups in our study were treated with broad-spectrum antibiotics ampicillin-sulbactam or amoxicillin-clavulanate, thus antibiotic choice on outcome could not be assessed in our study population.

Numerous studies have confirmed that the use of systemic steroids has a beneficial effect on the recovery of patients with COPD acute exacerbations (24-26). Systemic corticosteroids (oral or intravenous) have become a standard component in the pharmacotherapy of COPD exacerbations. In our study, group II was treated with concomitant corticosteroids in a high but not statistically significant ratio than group I. From our findings we can

deduct that steroids are used more frequently in patients with severe underlying lung disease for prompt resolution of symptoms but their use does not prevent relapses.

LTOT is a widely used treatment that improves survival in severe hypoxemic COPD patients (27,28). A recent study of Ringbaek et al, showed that in hypoxemic COPD patients, LTOT is associated with a reduction in hospital admission and in days spent in hospital (29). The results of the Medical Research Council study on a randomised-control group of COPD patients did not confirm the above findings with respect to LTOT (27). In our study, group I patients had a higher ratio of home oxygen use than group II patients, but the difference between the groups was not found to be statistically significant.

Many guidelines for COPD recommend influenza vaccination as a protective measure for these patients (30). The proportion of vaccinated individuals was low in both of our study groups. This low ratio is thought to be an outcome of our being a low-income country.

A limitation of our study was some minor errors in estimating the number of days between the two exacerbations. Exact information on number of days could not be obtained from all patients. In group II this was not important because the duration between the two episodes was short, but in group I the time was longer and some patients were not able to recall the number of days since their last exacerbation treated on an ambulatory basis. Seemungal et al (7) also reported that 50% of the exacerbations were not reported by the patients.

In summary, our study demonstrates that patients with severe COPD and high exacerbation frequency were more likely to have poor treatment outcome and therapeutic maneuvers did not have a major effect on treatment outcome.

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