

# THE ROLE OF INHALATORY CORTICOSTEROIDS AND LONG ACTING $\beta_2$ AGONISTS IN THE TREATMENT OF PATIENTS ADMITTED TO HOSPITAL DUE TO ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (AECOPD)

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## ABSTRACT

There is the question about the role of fixed combination of inhalatory corticosteroids and long acting  $\beta_2$  agonists in the treatment of patients admitted in hospital due to AECOPD.

The objective of this study is to determine the frequency of etiologic factors of AECOPD, to research the length of recovery time and the time free from exacerbation due to AECOPD at the patients treated with fixed combination inhalers containing F/S versus patients who were not treated with this combination.

This is retrospective-prospective, randomized, clinical study with a sample size of 70 patients who admitted to hospital due to AECOPD type I or II. Patients are randomized in two groups. Prospective group from 36 patients have been treated with oral or parenteral corticosteroids 7 – 14 days, other medications and fixed combination inhalers containing a F/S. Second, retrospective group from 34 patients have been treated with oral or parenteral corticosteroids 7 – 14 days (in time when we didn't have fixed combination inhalers containing a F/S) and other medications. In both groups (prospective and retrospective) the most frequent etiological factors of AECOPD was bacterial infection, after that viral infection, other factors as well as congestive heart failure. Average recovery time for symptoms of AECOPD was statistically significant shorter in group patients treated with fixed combination inhalers containing F/S (prospective group) than in group treated without this fixed combination. There are also significant differences in average number of days need for recovery in subgroups of patients by etiological factors of AECOPD, except in cases of AECOPD onset because of congestive heart failure. Average free time from exacerbation at the patients treated with fixed combination inhalers was statistically significant longer than in group of patients who were not treated with this combination.

In this study has demonstrated the presence of pathogenic bacteria in 53% our patients hospitalized due to AECOPD. There were 26% patients whose exacerbation is signed as viral origin. 11% cases had congestive heart failure. Average recovery time for non-viral AECOPD was 14,8 days and for exacerbations of viral origin 27,4 days. Average free time from exacerbation at the patients treated with fixed combination inhalers containing a F/S was statistically significant longer than in group of patients who were not treated with this combination. There were no statistically significant differences in average number of exacerbation during the year, between observed groups.

KEY WORDS: inhalatory corticosteroids, long acting  $\beta_2$  agonists, Acute Exacerbations of Chronic Obstructive Pulmonary Disease, treatment.

## INTRODUCTION

International guidelines have stated that reducing the frequency of exacerbations should be a primary target in the management of COPD. Up to 10% of acute hospital admissions in the UK are the results of exacerbations of COPD (1), and the mortality rate of these cases is around 11% during in-hospital stay, 43–46% within 1 year (2). The frequency of exacerbations is now known to have a major influence on the health status of patients (3) and probably the decline in lung function (4). There is convincing evidence that systemic corticosteroids improve health outcomes during COPD exacerbations. Their use improves health status, reduces dyspnoea, accelerates recovery of lung function, reduces length of hospitalisations and prevents relapses, which are very common in moderate-to-severe COPD. Several recently reported large multicentre trials evaluated the role of inhaled corticosteroids in preventing or slowing the progressive course of symptomatic COPD, (5, 6-8). In all of these trials, while there was no evidence for any reduction in disease progression, exacerbations were reduced by 12–25% depending on the severity and the definition used. These findings have been confirmed in studies of fixed combination inhalers containing a corticosteroids and a long-acting  $\beta_2$ -agonist. Both F/S and B/F combinations reduce exacerbation frequency to a greater extent than using a corticosteroid or long-acting  $\beta_2$ -agonist alone (9-11). Retrospective analyses of large databases suggest a possible effect of inhaled corticosteroids on reducing all-cause mortality in COPD patients and, by implication, some effect in reducing exacerbations (12-14). There is the question about the role of inhalatory corticosteroids and long acting  $\beta_2$  agonists in the treatment of patients admitted in hospital due to AECOPD.

## STUDY OBJECTIVES

- ◇ To determine the frequency of etiologic factors of AECOPD at the patients admitted to the hospital.
- ◇ To research the length of recovery time due to AECOPD at the patients treated with fixed combination inhalers containing F/S versus patients who were not treated with this combination.
- ◇ To determine the time free from exacerbation at the patients treated with fixed combination inhalers containing F/S versus patients who were not treated with this combination.

## PATIENTS AND STUDY DESIGN

This is retrospective-prospective, randomized, clinical study with a sample size of 70 patients who admitted to hospital due to AECOPD type I or type II. AECOPD had to be classified according to symptoms described by Anthonisen et al. (15) as follows. Type I who met all the following criteria: increase in amount of sputum, purulence of sputum and dyspnoea. Type II who met two of the above three criteria. Type III who met only one of the above criteria. All patients had similar co-morbidity. Patients are randomized in two groups. Prospective group from 36 patients have been treated with oral or parenteral corticosteroids 7 – 14 days, other medications and fixed combination inhalers containing F/S. Second, retrospective group from 34 patients have been treated with oral or parenteral corticosteroids 7 – 14 days (in time when we didn't have fixed combination inhalers containing a F/S) and other medications. Baseline and disease characteristics of the two groups were generally balanced (Table 1).

| Characteristic                                     | Prospective group<br>(n=36) | Retrospective group<br>(n=34) |
|--|-----------------------------|-------------------------------|
| Median age, years<br>(range)                       | 62,028 (48 – 73)            | 66,23 (46 – 82)               |
| Male, n, %   | 27 (75)                     | 22 (65)                       |
| Female, n, %                                       | 9 (25)                      | 12 (35)                       |
| Disease stage                                      |                             |                               |
| GOLD III, n, %                                     | 24 (67)                     | 15 (44)                       |
| GOLD IV, n, %                                      | 12 (33)                     | 19 (56)                       |
| Average number of<br>exacerbations by year<br>± SD | 2,47 ± 1,46                 | 2,59 ± 1,58                   |

TABLE 1. Baseline characteristics of observed groups

There were three conditions for inclusion and exclusion patients from study. All patients were not treated with antimicrobial agents before inclusion in study and all patients had the similar co-morbidity. Patients who died during the hospitalization are excluded from study. Before the start of hospital treatment, all patients' sputum's were taken for microbiological analysis. Bacterial origin of exacerbation has been made after demonstration of the presence the pathogenic bacteria in the sputum of patients. AECOPD associated with symptoms of common cold and without the presence of pathogenic bacteria's in sputum, signed as viral exacerbation. Following variables have been observed: the causes of AECOPD (bacterial infections, viral infections, congestive heart failure and other causes like smoking, inhalation of HCl fumes, etc), recovery time and free time to next exacerbation. Recovery time for symptoms was defined as the time from onset of the exacerbation to the day on which a 3-day moving average of the symptom score had returned to baseline.

Free time to next exacerbation was defined as the time between the onsets of the next exacerbation.

## STATISTICAL ANALYSIS

Qualitative variables are expressed as relative frequencies of categories. Numerical values are expressed as median (5<sup>th</sup>-95<sup>th</sup> percentile) because of their skewed distribution. Differences between groups were tested using the Kolmogorov-Smirnov test for categorical variables or the Tukey-Kramer test for numerical variables. Significance was defined as two-tailed p-value <0,05.

## RESULTS

In both groups (prospective and retrospective) the most frequent etiological factors of AECOPD was bacterial infection, after that viral infection, other factors as well as congestive heart failure. There were no statistically significant differences between groups in the frequency of etiological factors of AECOPD (Table 2).

Average recovery time for symptoms of AECOPD was statistically significant shorter at the group patients treated with fixed combination inhalers containing a F/S (prospective group) than in group treated without

|                     | <b>Bacteria's;<br/>n, %</b> | <b>Viruses;<br/>n, %</b> | <b>Others;<br/>n, %</b> | <b>Heart fail;<br/>n, %</b> |
|---------------------|-----------------------------|--------------------------|-------------------------|-----------------------------|
| Prospective group   | 19 (52,8)                   | 8 (22,2)                 | 3 (8,3)                 | 6 (16,7)                    |
| Retrospective group | 18 (52,9)                   | 10 (29,4)                | 5 (14,7)                | 1 (3,0)                     |
| Wilcoxon test       | T = 0,571                   |                          |                         |                             |
| ( $\alpha = 0,05$ ) | z = 0,2839                  |                          | NS                      |                             |

TABLE 2. Etiological factors of AECOPD

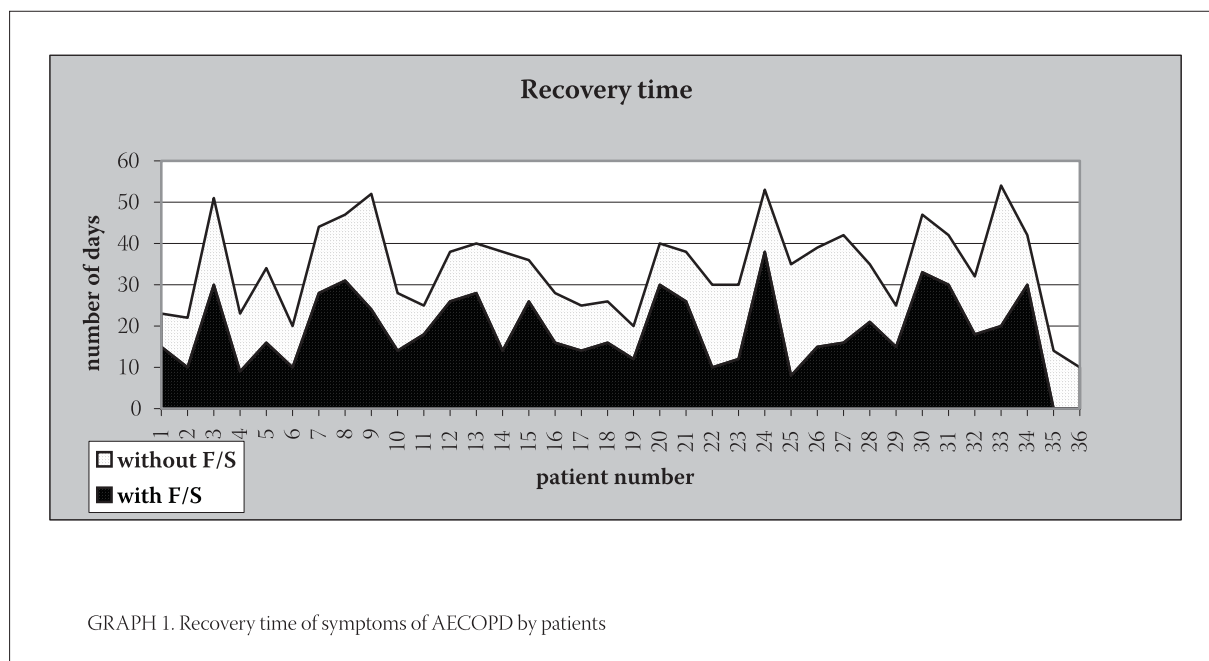
this fixed combination. There are also significant differences in average number of days need for recovery in subgroups of patients by etiological factors of AECOPD, except in cases of AECOPD onset because of congestive heart failure (Table 3 and Graph 1).

Average free time from exacerbation at the patients treated with fixed combination inhalers containing a F/S was statistically significant longer than at the group of patients who were not treated with this combination (Table 4, Graph 2).

There were also significant differences in average free time to the next exacerbation in subgroups of patients whose causes of AECOPD were viruses and other exogenous factors.

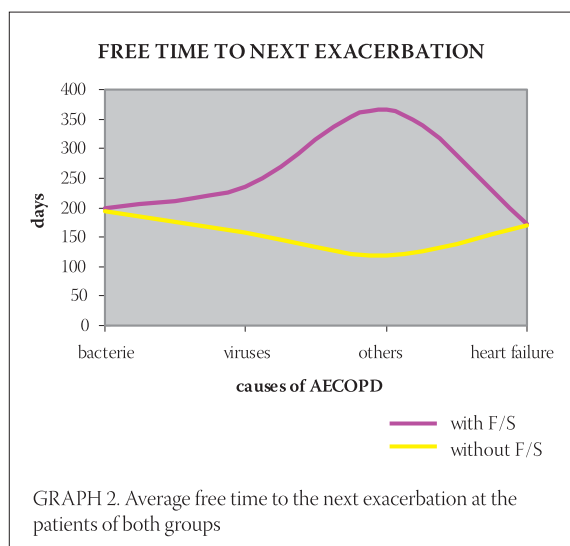
|                     | <b>Bacteria's</b> | <b>Viruses</b> | <b>Others</b> | <b>Heart failure</b> | <b>Average sum <math>\pm</math> SD</b> |
|---------------------|-------------------|----------------|---------------|----------------------|--|
| Prospective group   | 13,10             | 25,25          | 10,83         | 11,70                | 15,22 $\pm$ 6,52                       |
| Retrospective gr.   | 18,55             | 29,50          | 24,00         | 10,60                | 20,66 $\pm$ 8,27                       |
| Tukey-Kramer test   | q = 3,686         |                |               |                      |  |
| ( $\alpha = 0,05$ ) | p = 0,0136        |                | S             |                      |  |

TABLE 3. Average recovery time of symptoms of AECOPD by etiological subgroups



|                     | Bacteria's | Viruses | Others     | Heart failure | Average sum $\pm$ SD |
|---------------------|------------|---------|------------|---------------|----------------------|
| Prospective group   | 198,73     | 234,87  | 367,16     | 171,70        | 243,115 $\pm$ 164,20 |
| Retrospective gr.   | 193,33     | 156,50  | 118,00     | 169,00        | 159,20 $\pm$ 88,00   |
| Tukey-Kramer test   |            |         | q = 3,273  |               |                      |
| ( $\alpha = 0,05$ ) |            |         | p = 0,0334 | <b>S</b>      |                      |

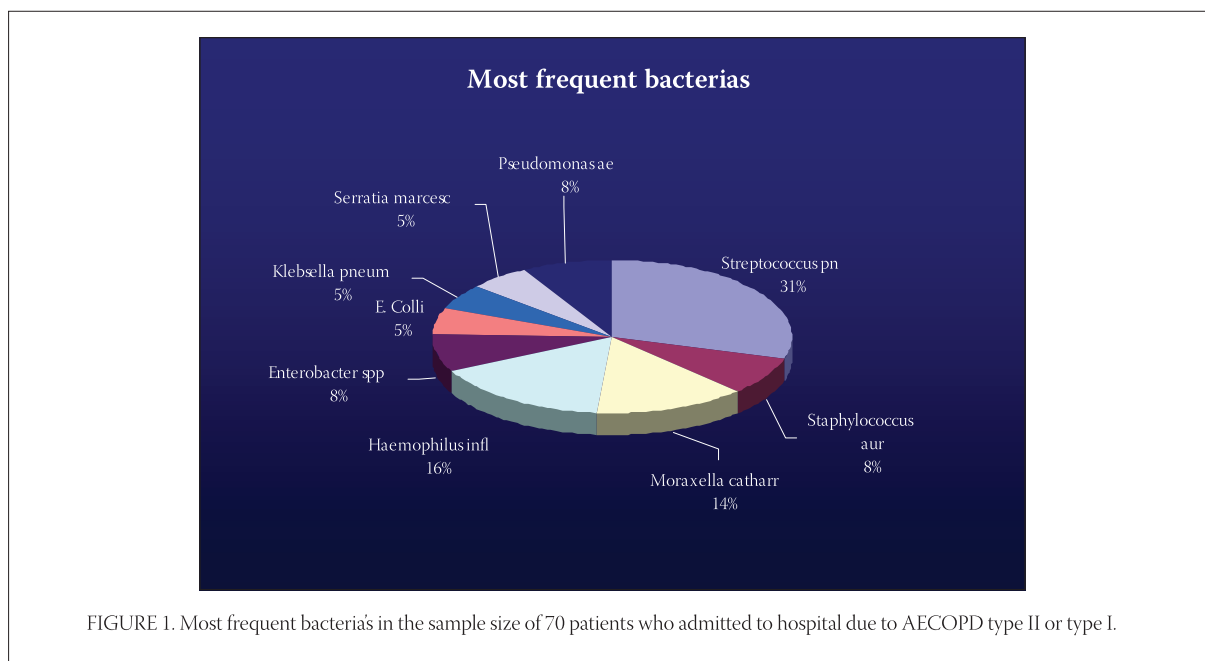
TABLE 4. Average free time to the next exacerbation at the patients of both groups



## DISCUSSION

Exacerbations of COPD are of major global importance. Exacerbations are an important outcome, not only because they pose a considerable economic burden but more importantly because repeated exacerbations of COPD lead to deteriorating health-related quality of life (3, 4) and, when associated with ventilatory failure, to premature death (2). Bacteria, viruses and environmental agents account for the vast majority of episodes

of exacerbation. In this study of patients admitted to hospital with severe exacerbations, 79% of patients had evidence of viral or bacterial infection. In study Papi et al. (16) there are 78% of patients with viral or bacterial infections. Bacteria are present in the cultured secretions of 30–40% of patients with chronic sputum expectoration and COPD even in the stable state. During exacerbations, the isolation rate increases to 50% (17). In this study has demonstrated the presence of pathogenic bacteria in 53% of exacerbations. The most frequent isolated bacteria were *Streptococcus pneumoniae* (in both groups), but there were isolated about two-fold more gram-negative bacteria's than gram-positive (in both groups too). From gram-positive bacteria's there were *Streptococcus pneumoniae*, *Staphylococcus aureus* (37,8% cases), and from gram-negative there were *Moraxella catarrhalis*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Enterobacter spp.*, *Escherichia coli*, *Serratia marcescens*, *Klebsella pneumoniae*, *Bacteroides spp.* (62,2% cases) (Figure 1). Approximately 50% of exacerbations are associated with upper respiratory tract virus infections and infection with rhinovirus, respiratory syncytial virus and influenza have been associated with exacerbations (18). Approximately 25% of patients admitted to hospital with an exacerbation of COPD had co-infection with bacteria and viruses (16). COPD patients with a history



of frequent exacerbations may be more susceptible to respiratory viral infections, although the nature of this susceptibility has not yet been defined. Rhinovirus can be recovered from the sputum more easily than from the upper airways, indicating that these viruses directly infect the lower respiratory tract (19,20). Unfortunately we don't have possibility to detect viruses from patients admitted to hospital due to AECOPD, so that our estimation of viral exacerbation is based on symptoms of common cold without the presence of pathogenic bacteria's in sputum. On that way there were 26% patients whose exacerbation is signed as viral origin. Heart failure may also lead to a symptomatic exacerbation of COPD, although it may be difficult to differentiate the symptoms of increased heart failure from those of a COPD exacerbation (21). In this study, as the etiological factor of AECOPD 11% cases had congestive heart failure. Tobacco smoking and inhalation of HCl fumes have been reason for AECOPD at the next 10% patients from the study. The costs of managing AECOPD are high, and it's particularly important that recovery time be shorter as much as possible. In the study Seemungal et al. (22) average recovery time was 15 days for 90% patients with non-viral AECOPD. In this study average recovery time for non-viral AECOPD was 11,87 days in prospective group (treated additionally with fixed combination inhalers containing a F/S) and 17,7 days in retrospective group, actually 14,8 days for both groups. It is very well known that increase symptoms induced by virus-associated exacerbations appear to last longer than bacterial exacerbations. For viral AECOPD in the same study Seemungal et al., for 90% patients average recovery time was 35 days. In this study its 25,25 days in prospective group and 29,5 days in retrospective group, actually 27,4 days for both groups (Table 3).

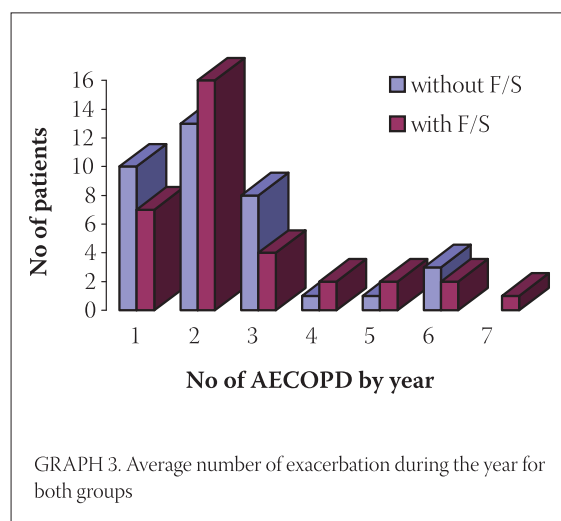
## CONCLUSION

In this study has demonstrated the presence of pathogenic bacteria in 53% our patients hospitalized due to AECOPD. The most frequent isolated bacteria were gram-positive bacteria's *Streptococcus pneumoniae*, and *Staphylococcus aureus* (37,8% cases), but there were isolated about two-fold more gram-negative bacteria's (62,2% cases). There were 26% patients whose exacerbation is signed as viral origin. 11% cases had congestive heart failure, and tobacco smoking and inhalation of HCl fumes have been reason for AECOPD at the next 10% patients.

Average recovery time for non-viral AECOPD was 14,8 days and for exacerbations of viral origin 27,4 days. Average recovery time was statistically significant shorter in subgroups patients treated with fixed combination inhalers containing a F/S in comparison with subgroups who were not treated with this combination.

Average free time from exacerbation at the patients treated with fixed combination inhalers containing a F/S was statistically significant longer than at the group of patients who were not treated with this combination. There were no statistically significant differences in average number of exacerbation during the year, between observed groups.

Observational studies performed in primary care centres observed that 16–22% of patients having exacerbations were admitted during 1 yr (23). Although several new classes of drug are in development for COPD, there are few clinical trials and little information about whether they prevent exacerbations. Between the others, study Wilson et al. (24) registered that steroids prolong time free from exacerbation. Study Jones et al. (25) also find reduction of exacerbations with fluticasone. Study Wouters et al. (26) conclude that F/S combination reduce exacerbation frequency to a greater extent than using a corticosteroid or long-acting  $\beta_2$ -agonist alone and prolong time to first exacerbation. In this study average free time from exacerbation at the patients treated with fixed combination inhalers containing a F/S was statistically significant longer than in group of patients who were not treated with this combination (Table 4, Graph 2) except subgroup patient with congestive heart failure. Even that there are no statistically significant differences in average number of exacerbation during the year, between observed groups ( $2,47 \pm 1,46$  vs.  $2,59 \pm 1,58$ ;  $q=0,405$ ,  $p=0,775$ ) (Graph 3).





### List of Abbreviations

|        |  |
|--------|--|
| AECOPD | Acute Exacerbations of Chronic Obstructive Pulmonary Disease |
| B/F    | budesonide/formoterol  |
| COPD   | Chronic Obstructive Pulmonary Disease                        |
| F/S    | fluticasone/salmeterol                                       |

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