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COPD exacerbation: influence of severity and type of systemic inflammation on the frequency of hospitalizations

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Abstract
Exacerbations of disease are recognized now to be an important predictor of the unfavorable prognosis for patients with COPD. This research aimed to identify presence and type of inflammation in patients who were hospitalized due to COPD acute exacerbation, in order to recognize factors, associated with frequent hospital admission. The retrospective analysis of 162 case histories of patients hospitalized due to COPD acute exacerbation during three years' period was carried out. The personal files of patients with single admission (group I – 112 persons) were separated from those who were hospitalized several times during three years' period (group II – 19 persons). Anthropometric parameters, including body mass index (BMI), data of post-bronchodilators' pulmonary function tests (FEV1, FVC and FEV1/FVC), whole blood count, serum total and C-reactive protein, urine tests on time of admission to the in-patient unit were studied in all patients. The vast majority of patients with COPD acute exacerbation had clinical and laboratory signs of systemic inflammation. In more than in half cases it was neutrophilic (65.18 ± 4.50% and 57.89±11.33% in group I and II respectively), regardless the number of hospitalizations. Significantly higher C-reactive (11.51 ± 4.80 vs. 9.03 ± 3.58 mg/ml) and total (73.00 [71,00-78,00] vs 69.00 [65.00-73.00] g/l) protein and a higher percentage of patients with an increased number of eosinophils (10.53 ± 7.04% vs 0.89 ± 0.89%) was found in group of patients who were hospitalized repeatedly compared with the group of hospitalized only once. Thus, high levels of C-reactive protein, total protein and eosinophilia during exacerbations may be considered as predictors of frequent hospitalizations in patients with COPD.

Keywords: COPD, exacerbation, systemic inflammation, hospitalization rate.

1. Introduction
Chronic obstructive pulmonary disease (COPD) is one of the major causes of morbidity, and it was the third leading cause of mortality worldwide in 2010 [1]. Exacerbations of disease are recognized now to be an important predictor of the unfavorable prognosis for patients with COPD [2, 3]. Small portion of patients suffering from frequent exacerbations (approximately 10%), accounting for more than 70% of the total cost of COPD treating due to need to stay in hospital and emergency care [4]. In the year of 2005 it was estimated that COPD exacerbations cost 38 billion dollars to the US health care system [5].
Re-hospitalizations due to COPD exacerbation call for special attention, because it has been established that expenditures in re-hospitalization are significantly greater than in case of initial hospital stay [6]. On average, costs for a 30-day readmission with COPD as principal diagnosis ($8,400) were 18 percent higher than for the index stay ($7,100). Costs were more than 50 percent higher for the readmission with COPD as any diagnosis ($10,900) or for all-cause readmissions ($11,100) [6].
The COPD exacerbations exceptional significance was reflected in the GOLD, 2011 [7]. In this document, even in the definition of COPD, stressed that exacerbations and comorbidities significantly affect the severity of diseases in some individuals. In addition, in GOLD, 2014 not only number of exacerbations, but also number of hospitalizations during the past year has been recognized as one of the main criteria for the patients' future risks detection [8]. A similar approach was adopted in Order number 555 of the Ministry of Health of Ukraine (June 27, 2013) [9], which now governs the provision of medical care to patients with COPD in our country. Nevertheless, since in some cases re-hospitalization could be avoided, it is important to determine predictors of returning to the hospital due to COPD exacerbation. Their identification seems to be useful for planning the future medical intervention strategy in patients with COPD. This strategy may include either increasing the dose of medication that

the patient is already receiving, or prescription of additional drugs, i.e. anti-inflammatory agents. Meanwhile, existing criteria predict probability of re-hospitalization due to COPD exacerbation too approximately. At the same time, in order to react to possible worsening of the patient's condition effectively, practitioners should have a simple and reliable way of predicting the probability of the hospitalization.

Since systemic inflammation is one of the leading mechanisms of COPD occurrence and progression, and its expression can greatly influence the nature and extent of medical intervention in disease [7-12], this research aimed to identify presence and type of inflammation in patients who were hospitalized due to COPD acute exacerbation, in order to recognize factors, associated with frequent hospital admission.

2. Material and methods

The retrospective analysis of case histories of patients hospitalized to therapeutic unit in Municipal establishment "Dnipropetrovsk clinical hospital №6" of Dnipropetrovsk Regional Council" during three years' period was carried out. Inclusion criterion for analysis of chosen case histories was verified diagnosis «COPD exacerbation» according to the Order №128 of Ministry of Health of Ukraine from 19.03.2007 [13], taking into account findings of post-bronchodilatation spirometry according to international standards of quality and recommendations of Ukrainian scientists [14, 15]. Criterion for case histories exclusion was presence of clinical-X-ray signs of pulmonary infiltration, pulmonary atelectasis or the pleural effusion in time of hospitalization.

During the analysis the personal files of patients with single admission were separated from those who were hospitalized several times during three years' period. Anthropometric parameters, including body mass index (BMI), data of post-bronchodilators' pulmonary function tests (FEV1, FVC and FEV1/FVC), whole blood count, serum total and C-reactive protein, urine tests on time of admission to the in-patient unit were studied in all patients.

The results obtained were processed using descriptive and analytical statistics by means of «STATISTICA 6.1» program [16]. Number of observations (n) was calculated for all findings. Mean values (M) for quantitative signs and root-mean deviations (± SD) under conditions of a normal distribution or median (Me) and upper and lower quartiles ([25-75%]) under conditions of abnormal distribution of findings were defined. Qualitative signs were presented in the form of absolute values (n) and relative frequencies (P), expressed in the share of unit or in percentage (%), with marking of an error (± m). Significance of differences in quality parameters was evaluated mostly by chi-square ($\chi 2$) and when $n < 5$ – by Fisher's exact criterion for frequency. The correlation between indicators (quantitative, qualitative) was assessed using Spearman correlation coefficient (R) regardless of their distribution. To assess the significance of differences between correlation coefficients in the two groups the "correlation coefficients for errors' test" was used. For analysis of all types findings differences between the groups were considered to be significant if $p < 0.05$.

3. Results and discussion

162 case histories with diagnosis of COPD exacerbation requiring hospitalization, confirmed by clinical, anamnestic and spirometry findings, were selected for the final analysis. Detailed study elucidated that in 112 cases (69.14 ± 3.63%) patients were hospitalized only one time during three years' period. However, almost third part of hospital stay due to COPD exacerbation, 50 (30.86 ± 3.63%), was caused by hospitalization of the same persons. So, we separate two groups of patients: group I (112 persons) – hospitalized one time and group II (19 persons) – hospitalized due to COPD exacerbation two or more times during three years' period.

In accordance with retrospective analysis data (Table 1), both groups were similar regarding to age, sex and anthropometric characteristics.

The vast majority of hospitalizations in both groups were associated most likely with infectious exacerbation. It was evidenced by the presence of fever at the time of hospital admission in approximately 9/10 of patients both in group I and in group II.

Table 1: Anthropometric data and clinical and laboratory signs of systemic inflammation in patients who were hospitalized due to exacerbation of COPD

Indexes	Group I (n = 112)	Group II* (n = 19)	p
Sex: men, n (P [95 % CI]) 2) women, n (P [95 % CI])	79(0.71 [0.62-0.78]) 33(0.29 [0.22-0.38])	16 (0.84 [0.60-0.96]) 3(0.16 [0.05-0.40])	0.239 0.239
Age Med [25%-75%], years	65.00 [55.00-69.00]	59.00 [53.00-73.00]	0.882
Height M ± SD, cm	169.45 ± 8.46	171.26 ± 8.01	0.387
Weight Med [25%-75%], kg	75.00 [69.00-85.00]	70.00 [60.00-90.00]	0.253
BMI Med [25%-75%], kg/m^2	26,12 [23,62-29,73]	25,71 [20,78-28,38]	0,137
Fever, n (P ± m %)	108(96.43 ± 1.75)	17(89.7 ± 7.04)	0.209
Total serum protein, Med [25%-75%], g/l	69.00[65.00-73.00]	73.00[71,00-78,00]	0.017
Serum C-reactive protein, M ± SD, mg/l	9.03 ± 3.58	11.51 ± 4.80	0.012
White blood cells, Med [25%-75%], *10^9 cells/l	11.80[10.50-12.90]	12.20[9.90-13.70]	0.849
Type of inflammation (in accordance with whole blood count): Neutrophilic, n(P ± m %)Eosinophilic, n(P ± m %) Lymphocytic, n(P ± m %)Monocytic or basophilic, n (P ± m %)No inflammation, n(P ± m %)	73(65.18 ± 4.50) 1(0.89 ± 0.89) 24(21.43 ± 3.88) 0(0 ± 0,00) 15(13.39 ± 3.22)	11(57.89±11.33) 2(10.53 ± 7.04) 3(15.79 ± 8.37) 0(0 ± 0,00) 3(15.79 ± 8.37)	0.235 0.009 0.416 1.000 0.506

Note. * – data of the group II concern first registered hospitalization.

Plasma C-reactive protein was higher than 5 mg/l (upper limit of normal ranges in the local laboratory) in majority of patients of both groups: in 75 (66.96 ± 4.44%) cases in group I and in 16 (84.21 ± 8.37%) – in group II (Figure 1). This indicates the presence of systemic inflammation's signs during COPD acute exacerbations in the most of patients, admitted to the therapeutic unit. Number of persons with C-reactive protein which exceed normal ranges was higher in group II, although the difference with group I was not statistically significant ($p = 0.131$). However, the average level of C-reactive protein was significantly higher in patients who admitted to the hospital due to COPD exacerbation many times (Table 1). Therefore abnormal serum C-reactive protein during exacerbation could be considered as a possible predictor of repeated hospitalization in patients with COPD.

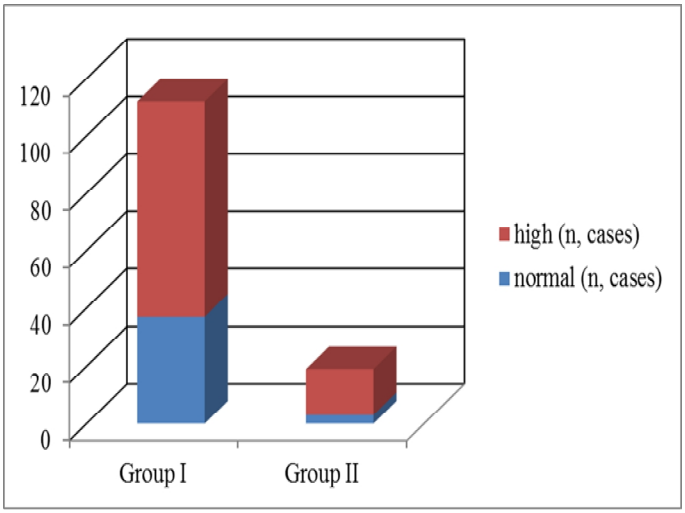

Fig 1: Proportion of patients with normal and high serum C-reactive protein in groups

Total protein in serum was determined in all patients at the beginning of hospitalization. According to a retrospective analysis data, none of the patients in both groups had elevated total protein level. At the same time, hypoproteinemia was observed in 20 (17.86 ± 3.62%) cases of group I and in 2 (10.53 ± 7.04%) of group II ($p = 0.340$). However, significant proteinuria was not found in urinalysis in any of the patients, regardless of group. In this reason, decreasing of total protein in some patients cannot be explained by loss of protein due to kidney damage. Unfortunately, there were no data of detailed blood protein spectrum in case histories, so we can only assume that hypoproteinemia, even against the background of systemic inflammation, was caused by significant catabolic processes in the body of some patients with acute exacerbation of COPD. This assumption was confirmed by the fact that in the group of patients who had been hospitalized several times over three years, the level of total protein significantly ($p = 0.027$) moderate ($R = 0.609$) correlated with body BMI. I general the median level of total serum protein in both groups although were within normal limits, but nevertheless were significantly higher in group II (Table 1). These results require further investigations and may be clarified only after detailed qualitative serum protein analysis in patients with acute exacerbation of COPD.

Whole blood count investigation had found the high white blood cells level in 96 (85.71 ± 3.31%) patients of group I and in 16 (84.21 ± 8.37%) patients of group II. It confirms the hypothesis of infectious nature of COPD acute exacerbation in most hospitalized patients. At the same time the number of leukocytes in peripheral blood was within the normal ranges in approximately 15% of patients in both groups. No case of leucopenia either in group I, or in group II was recorded. Overall, the median total number of white blood cells exceeded the normal values in each of group, but the difference between this parameter in group I and II was not statistically significant.

As the systemic inflammation implemented with the participation of many cells during COPD acute exacerbation, it was appropriate to determine the type of inflammation evaluating the number of neutrophils, eosinophils, lymphocytes, monocytes and basophils in whole blood count (Table 1).

None of the patients has increased or decreased basophils and monocytes number regardless of the group. At the same time, nearly one in five patients in groups I and one in six in group II had lymphocytosis, which apparently was associated with acute viral infection as a likely factor that provoked exacerbation. The most numerous were patients with a high percentage of neutrophilic leukocytes, regardless the group to which they belonged. This fact probably reflects the bacterial nature of COPD acute exacerbation. The information that needs attention is significantly larger share of patients with eosinophilic type of systemic inflammation in the group with recurrent hospitalization, while in the group I there was only one patient with blood eosinophilia. Therefore, one should pay attention to the elevated levels of eosinophils in the peripheral blood when determining the possible predictors of re-hospitalization due to COPD exacerbation.

4. Conclusions

1. The vast majority of patients with COPD acute exacerbation had clinical and laboratory signs of systemic inflammation. In more than in half cases it was neutrophilic (65.18 ± 4.50% and 57.89±11.33% in group I and II respectively), regardless the number of hospitalizations.
2. Significantly higher C-reactive (11.51 ± 4.80 vs. 9.03 ± 3.58 mg/ml) and total (73.00 [71,00-78,00] vs 69.00 [65.00-73.00] g/l) protein and a higher percentage of patients with an increased number of eosinophils (10.53 ± 7.04% vs 0.89 ± 0.89%) was found in group of patients who were hospitalized repeatedly compared with the group of hospitalized only once. Thus, high levels of C-reactive protein, total protein and eosinophilia during exacerbations may be considered as predictors of frequent hospitalizations in patients with COPD.

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