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EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND THE EFFICACY OF VARIOUS ANTIMICROBIAL REGIMENS OF TREATMENT

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The task of this study was to assess whether the empirical administration of different antibiotics for exacerbations of chronic bronchitis and chronic obstructive pulmonary disease (COPD) in the primary-care setting is associated with a different clinical course, principally related to the speed of onset of action. The study included 252 patients diagnosed with an exacerbation of chronic bronchitis or COPD. All patients have been studied for 30 days, with an intermediate visits every 10 days at which they were asked about the duration of the symptoms; the presence of symptoms was assessed at 3, 5 and 10 days. Three antibiotic regimens were evaluated: amoxicillin/clavulanic acid 500 mg/125mg three times a day for 10 days, Ciprofloxacinum 500 mg twice a day for 5 days, or Rovamycinum 3000000 IU twice a day for 10 days.. The clinical cure rate, defined as the remission of the three cardinal symptoms of exacerbation (increased expectoration, change in sputum purulence, and increased dyspnoea) were similar on the tenth day: 67% in the group receiving Ciprofloxacinum, 65% in those taking Amoxicillin/clavulanic acid, and 64% in those taking Rovamycinum (p = 0.38). However, differences in the clinical cure rates were observed on day 3 (Ciprofloxacinum 20 %, Amoxicillin/clavulanic acid 9.6 %, and Rovamycinum 6.5 %) and day 5 (Ciprofloxacinum 49%, Amoxicillin/clavulanic acid 26.5% and Rovamycinum 30 %). The cure rates were significantly higher in the Ciprofloxacinum group than in either of the other two treatment groups (p<0.001 for both days).

***Key words**: exacerbation of chronic bronchitis, chronic obstructive pulmonary disease, antimicrobial regimens.*

INTRODUCTION

Chronic pulmonary disease, particularly chronic bronchitis and chronic obstructive pulmonary disease (COPD), represents one of the principal demands on healthcare in primary care. According to recent studies, it is estimated that in Ukraine up to 8-10% of the population > 40 years of age may be affected by COPD [1; 2]. In men >65 years of age this figure may rise to 20% [2].

The course of both chronic bronchitis and COPD can be affected by episodes of worsening of respiratory symptoms, known as exacerbations. The aetiology of exacerbations is still a matter of controversy. Since respiratory secretions in some patients with stable COPD carry significant concentrations of potentially pathogenic micro-organisms, the isolation of such micro-organisms during exacerbations should not be interpreted as a conclusive demonstration of their pathogenic role. However, studies performed with specific invasive techniques have shown that both the number of patients with pathogenic bacteria in respiratory secretions and the number of colony-forming units increase during exacerbations [3]. Furthermore, the local inflammatory response of the host increases with increasing airway bacterial load [4]. According to reported findings, a high percentage of exacerbations, between 50 % and 70 %, are of infectious origin [5]. *Haemophilus influenzae* is the most frequently isolated bacterium, followed by *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa* [6-8]. Viral infections, particularly influenza and

parainfluenza viruses, rhinovirus and adenovirus, may cause up to 30 % of episodes of infectious exacerbation [9].

It has been known for many years that the presence of at least two of the three cardinal symptoms of exacerbation [10] (the criteria: increased sputum, increased dyspnoea, and change in the colour of sputum) indicates that the patient would benefit from and the condition would be appropriate for antibiotic treatment, particularly when the sputum has a purulent appearance coinciding with the episode. A recent study demonstrated that patients with COPD experience a mean of two exacerbations per year, of which 90 % are treated with antibiotics in the primary healthcare setting [2].

The task of this study was to define the clinical course of patients with exacerbations of chronic bronchitis or of COPD in this setting, and to evaluate the time-course of the clinical improvement, comparing three different antimicrobial regimens.

PATIENTS AND METHODS

This was an observational study of patients with chronic bronchitis or COPD being followed up in primary-care centres at the region of Sumy Clinical Hospital № 1. The study was carried out between February 2011 and May 2012 in 252 patients. In order to establish a diagnosis of chronic bronchitis, it was required that the patient have a productive cough for at least 3 months per year for 2 consecutive years; for a diagnosis of COPD, the observation of a non-reversible airflow obstruction was required, characterised on forced spirometry by a forced expiratory volume in 1 second (FEV_1) < 80 % of the theoretical value and an FEV_1/forced vital capacity (FVC) ratio of < 70 % in a stable phase [2]. Clinical diagnosis was based on the judgement of the doctor treating the patient. Diagnosis of an exacerbation was defined by the patient's symptoms: increase in the usual level of dyspnoea, increase in sputum volume, and/or increase in sputum purulence [10]. Exacerbations having one of the symptoms were classified as type III, those with two symptoms as type II, and those with all three symptoms as type I [10]. Probable bacterial aetiology was established when the exacerbation was Anthonisen type I or II, or when sputum purulence was present.

Patients with bronchial asthma, cystic fibrosis, bronchiectasis, malignancy or pneumonia and patients who fulfilled criteria for hospitalisation were excluded.

After diagnosis of the exacerbation, the doctor was free to prescribe any of the three following options of antibiotic treatment: Amoxicillin/clavulanic acid 500mg /125mg three times a day for 10 days, Ciprofloxacinum 500 mg twice a day for 5 days, or Rovamycinum 3000000 IU twice a day for 10 days, in accordance with current guidelines [2]. All patients were given appointments 10 days after the first visit, at which they were asked about the number of days that had elapsed from starting the antibiotic until resolution or return to baseline severity of the following symptoms: dyspnoea, volume of expectoration, purulence of the expectoration, and cough. The investigator evaluated the course of the exacerbation as a function of the resolution of the symptoms; the treatment was considered to have been successful if cure or clinical improvement was achieved. Cure was defined as the complete resolution of the three cardinal symptoms of exacerbation [10].

DATA COLLECTION AND ANALYSIS

All the data generated were collected on a form in electronic format designed specifically for the study; this form included information on demographic variables, respiratory risk factors, co-morbidity, characteristics

of the patients' respiratory disease, degree of dyspnoea (0 = no dyspnoea; I = dyspnoea when climbing two floors; II = dyspnoea when climbing one floor; III = dyspnoea when walking on flat ground; IV = resting dyspnoea), usual medication, characteristics of the exacerbation, and treatment administered. The form was loaded into a portable personal handheld computer (PCA).

A descriptive analysis was performed, followed by a survival analysis using the Kaplan-Meier methods, and an evaluation of the relationship between evolution of symptoms and antimicrobial treatment using the Kruskal-Wallis test. The Wilcoxon rank sum test was used for paired comparisons between groups, and significance was considered with a p-value of <0.017, adjusted for multiple comparisons. With a sample of 84 patients per group, our study had a power of 98 % to detect a significant difference of 1 day in resolution of symptoms between any of the given treatments, considering a standard deviation of 3 days and a global significance of 0.05. The x^2 test was used to compare qualitative variables. A p-value of <0.05 was taken as significant. The SAS version 7.0 software package for Windows 95 was used to perform the analyses.

RESULTS

The demographic characteristics of the patients are summarised in the table 1.

*Table 1 – Clinical and demographic characteristics of the study of the patients (n = 252)**

	Total Population	Amoxicillin/ clavulanic acid	Cipro-floxacinum	Rova-mycinum	p-Value
Age (y)	48	49	48	48	0.89
Males (%)	71	73	70	69	0.76
Duration of chronic bronchitis / COPD (y)	12	12	11	12	0.72
Proportion of patients with >2 co-morbidities (%)	26	24	25	26	0.36
Smokers end ex-smokers (%)	79	79	80	76	0.74
Pack-years	22	22	23	21	0.75
Pulmonary function tests :					
FVC (ml)	3578	3581	3352	3574	0.12
FVC (%)	74	76	73	72	0.61
FEV_1 (ml)	2313	2324	2350	2263	0.94
FEV_1 (%)	61	62	61	61	0.52
FEV_1 / FVC	64	65	65	63	0.60
No / during year prior to enrolment of:					
exacerbations	2.4	2.6	2.4	2.4	0.02
visit to GP	5.9	6.2	5.5	6.1	0.02

* Data are expressed as mean (SD) unless otherwise specified. p-Values are with respect to the results of the comparison between the three groups. Kruskal – Wallis test and chi-squared test when appropriate.
FEV_1 – forced expiratory volume in 1 second;
FVC – forced vital capacity;
GP – general practitioner

The majority were males (71 %) and the mean age of the population was 48 years (SD 9.8 years). Of the patients with spirometry, the median FEV_1 was 61 % (SD 14 %), signifying a moderate alteration in pulmonary function.

Treatment of the diseases exacerbations: Patients were included in the study on developing an exacerbation. An increase in dyspnoea was observed in 89 % of patients, and 86 % presented with an increase in sputum purulence. Globally, 23,4 % of the exacerbations were classified as type I, 60,7 % as type II, and 15,9 % as type III. The antibiotic treatment administered was Amoxicillin/clavulanic acid in 83 patients (32,9 %), Ciprofloxacinum in 85 patients (34 %), and Rovamycinum in 84 patients (33 %). The principal clinical and demographic characteristics of the patients receiving the different antibiotics are shown in table 1; there were no significant differences between the three treatment groups. The severity of the exacerbations was also similar in the three treatment groups (table 2).

Table 2 - Severity of exacerbations and clinical response to antibacterial therapy (Data are expressed as percentages)

	Pacients:	Type of exacerbation *			Clinical success**	Cure rate***
		I	II	III		
Ciprofloxacinum	23.4	22.6	62.0	15.4	97.6	67.9
Amoxicillin/clavulanic acid	60.7	23.8	59.5	16.7	91.7	66.7
Rovamycinum	15.9	23.8	60.7	15.5	94.0	64.3
p-Value****		0.89			0.40	0.38

** Type of exacerbation – is defined according to the Anthonisen et all classification.*
*** Clinical success is defined by the medical doctor and includes clinical cure and improvement in symptoms.*
**** Cure rate is the proportion of patients with no symptoms of exacerbation at day 10.*
***** p-Value according to the Kruskal-Wallis test*

The percentage of cure at day 10 was similar in the three groups: 67,9 % for Ciprofloxacinum versus 66,7% for Amoxicillin/clavulanic acid and 64,3 % for Rovamycinum, with no significant differences being found (table 2).

Speed of Action of the Antibiotic Treatment: Sputum purulence resolved in 89 %, 89 % and 86 % of patients treated with Ciprofloxacinum, Amoxicillin/clavulanic acid, and Rovamycinum respectively. The expectoration resolved in 87 %, 88 % and 86 % of the patients, with each treatment, respectively, and the dyspnoea resolved in 82 %, 81 % and 81 % of the patients, respectively. No statistical significance was observed between the different treatments in any of these analyses.

In contrast, statistically significant differences were found between the different antimicrobial treatments on analysis of the mean number of days to resolution of the symptoms. The mean time to relief of symptoms was 6 days with Rovamycinum, 5.9 days with Amoxicillin/clavulanic acid and 4.8 days with Ciprofloxacinum. Pairwise comparisons showed significant differences between Ciprofloxacinum and the other treatments ($p < 0.0001$ for Ciprofloxacinum vs both Amoxicillin/clavulanic acid and Rovamycinum) and no differences between Amoxicillin/clavulanic acid and Rovamycinum ($p = 0.94$). The mean time to resolution of sputum purulence was 3.4 days in the group treated with Ciprofloxacinum, shorter than that observed in the

groups treated with the other antibiotics (4.1 days for Amoxicillin/clavulanic acid and 3.8 days for Rovamycinum; p = 0.018 for Ciprofloxacinum vs both Amoxicillin/clavulanic acid and Rovamycinum). Similar results were observed on comparison of the time to resolution of the increase in the quantity of sputum. With respect to symptoms of cough, dyspnoea and fever, the patients treated with Ciprofloxacinum once again showed a consistently more rapid recovery, although, in these cases, the differences did not reach statistical significance (table 3).

*Table 3 - Days to resolution of clinical signs/ symptoms**

Symptom	Ciprofloxacinum	Amoxicillin/ clavulanic acid	Rovamycinum	p-Value**
Volume of expectoration	3.8	4.6	4.4	0.019
Purulence of expectoration	3.4	4.1	3.8	0.018
Dyspnoea	3.8	4.6	4.6	0.21
Fever (> 38 °C)	2.0	2.3	2.4	0.89
Cough	4.2	4.8	4.9	0.15

*Data expressed as mean (SD) number of days to resolution.
**Results of the comparison between the three groups (Kruskal –Wallis test)

The proportion of patients considered cured after 3 days of treatment was 20 % in the patients treated with Ciprofloxacinum, 6.5 % in the patients treated with Rovamycinum, and 9.6 % in the patients treated with Amoxicillin/clavulanic acid (p < 0.001 in favour of Ciprofloxacinum vs both Rovamycinum and Amoxicillin/clavulanic acid). These differences persisted after 5 days of treatment: Ciprofloxacinum 49 %, Amoxicillin/clavulanic acid 26.5 % and Rovamycinum 30 % (p < 0.001 in favour of Ciprofloxacinum vs both Rovamycinum and Amoxicillin/clavulanic acid), but at 10 and 30 days the cure rates had equalised for the three treatments (figure 1).

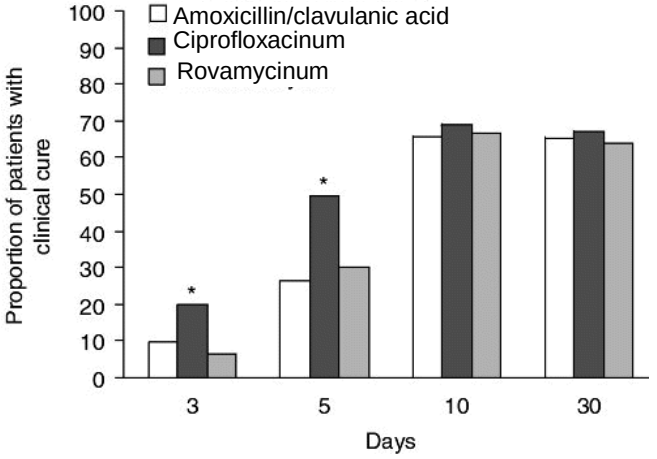

Figure 1 – Proportion of patients achieving clinical cure over the study period, grouped according to antimicrobial treatment prescribed.
** p < 0.001 in favour of Ciprofloxacinum versus both other treatments*

DISCUSSION

The results of the present study indicate that although the clinical cure rates achieved with the three antibiotic regimens for treatment of exacerbations of chronic bronchitis and COPD are similar at the end of treatment, the time-course of the recovery is significantly different on using Ciprofloxacinum, since this treatment achieves a more rapid resolution of the symptoms. To achieve a more objective evaluation of recovery than that provided by the clinical judgement of the different investigators, clinical cure rates were used, with cure defined as the disappearance of the three cardinal symptoms of exacerbation. Using this definition, it was observed that the cure rates at 3 and 5 days after starting treatment were significantly higher in patients treated with Ciprofloxacinum than in those treated with Amoxicillin/clavulanic acid or Rovamycinum.

The three patient groups analysed were perfectly balanced in all their demographic, clinical and functional characteristics, as well as in the severity of the exacerbations. Another argument in favour of the similarity of the three groups is that the cure rates achieved at 10 and 30 days were similar between treatment groups. Relapses between days 10 and 30 appeared to be very infrequent. In this study clinical cure was defined as a complete relief of symptoms and did not include improvement of symptoms. Patients who achieved a cure were probably less likely to relapse than those who experienced only an improvement in symptoms.

Since time to recovery was investigated at the control visit at day 10, some recall bias may have interfered with the results; however, if it did exist, this bias would affect all three treatment arms. In addition, the time to recovery obtained in this study was similar to that observed in another study using a different methodology [11], therefore providing validity to the results.

Some patients with type III exacerbations were included in the study as the medical doctor indicated the need for antibiotic therapy. In most cases sputum purulence was the only symptom present, which was an inclusion criterion in the study. This should, however, not influence the results, since the percentage of type III exacerbations was similar in the three antibiotic arms. Furthermore, the inclusion of patients who would not benefit from antibiotics decreases the possibility of finding differences between groups. Therefore, excluding these cases would result in even higher differences in the outcomes between antibiotics.

Our study looks closely at a very important aspect and one that must be taken into consideration in the treatment of exacerbations: the speed of symptomatic cure. This aspect has not been studied in detail until very recently; the majority of clinical trials with antibiotics analyse therapeutic efficacy at 7-10 days and, at this time-point, they usually find equivalent results between various antibiotic options, a finding that also occurred in our study 10 days after starting antimicrobial treatment. However, it is possible that one antibiotic achieves higher rates of clinical cure in the first 3-4 days of treatment and the comparator in the following 5-7 days. This very significant difference is often not evaluated or reported in comparative studies. Moreover, faster improvement of the cardinal symptoms of cough and phlegm may have an impact on the patient's well-being, since a recent study demonstrated that these two symptoms are important predictors of health status in smokers. Through a speedier recovery from their respiratory symptoms, the patients may avoid repeat visits to the doctor, symptomatic medication, and even a further course of antibiotics or substitution of the antibiotic if lack of efficacy is suspected.

The treatment of exacerbations of chronic bronchitis with Ciprofloxacinum is associated with a marked rapidity of resolution of the volume and purulence of sputum. In a recent study, patients who received

Ciprofloxacinum presented an eradication rate of 63 % of the causative pathogens of the exacerbation on the third day of treatment, compared with 48 % in patients treated with azithromycinum (p = 0.11) [12]. The explanation for the greater speed of action is based on the pharmacokinetic and pharmacodynamic characteristics of the antibiotic, which result in a more rapid elimination of respiratory pathogens. In a recent study carried out in Spain, it was observed that 95.5 % of the patients receiving this fluoroquinolone had recovered from their symptoms of exacerbation within 5 days of starting treatment [13]. In a comparative study of 441 patients with exacerbations of COPD, patients treated with moxifloxacin experienced symptoms for a mean of 1.2 days less than those treated with co-amoxicillin/clavulanic acid, cefuroxime or clarithromycinum; this difference was statistically significant (p = 0.006) and, in a multivariate analysis, treatment with moxifloxacinum was the only variable independently and significantly associated with a shorter duration of the symptoms of exacerbation (p = 0.02) [11].

The implied relationship between rapid and effective bacteriological eradication and clinical cure has been demonstrated in various studies. In one of these, in which the risk of therapeutic failure was compared in patients treated with amoxicillin (an antibiotic considered to be first-line treatment) or other agents such as co-amoxicillin/clavulanic acid, cephalosporins and quinolones, it was observed that treatment of the exacerbation with the aminopenicillin, amoxicillin, to which *Haemophilus influenzae* and *Moraxella catarrhalis* are frequently resistant, carries an increased relative risk of failure of 3.4 compared with the other antimicrobial agents [14]. In a clinical trial comparing moxifloxacin with clarithromycin, it was observed that the rate of clinical cure was similar for the two treatment groups; however, the patients treated with moxifloxacin achieved a global bacterial eradication of 77 % compared with 62 % with the macrolide at day 7; a difference of 15 % (95 % CI 8.5-27.7 %), and against *Haemophilus influenzae*, an eradication rate of 90.9 % was reported with moxifloxacin and 53.5 % with clarithromycin. The speed of symptom resolution was not evaluated in this study [15]. This lower efficacy observed with the macrolide may be explained by the high rates of resistance shown by *Haemophilus influenzae* to these antibacterial agents. At present, 35 % of *Haemophilus influenzae* strains isolated from the respiratory tract are resistant to macrolides [16; 17].

All these results support the quantitative hypothesis that implies the existence of a threshold concentration of micro-organisms above which the inflammatory reaction gives rise to symptoms of exacerbation. Consequently, it is sufficient to reduce the number of colonies, without complete eradication, in order to achieve remission of the symptoms and clinical cure; this increases the risk of continued, residual colonisation in patients who have recovered from the exacerbation.

Although it may not be surprising that Ciprofloxacinum achieves a more rapid improvement in symptoms than Rovamycinum because of its greater bacteriological efficacy, its superiority to Amoxicillin/clavulanic acid is of particular importance.

CONCLUSION

The results of this study suggest that the antibiotic treatment of exacerbations of chronic bronchitis and COPD with Ciprofloxacinum is associated with a more rapid remission of the symptoms to that achieved with Amoxicillin/clavulanic acid or Rovamycinum.

ЗАГОСТРЕННЯ ХРОНІЧНОГО ОБСТРУКТИВНОГО ЗАХВОРЮВАННЯ ЛЕГЕНЬ ТА ЕФЕКТИВНІСТЬ РІЗНИХ РЕЖИМІВ АНТИБАКТЕРІАЛЬНОЇ ТЕРАПІЇ

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Метою даного дослідження було порівняння ефективності лікування пацієнтів, які страждають на хронічне обструктитвне захворювання легень (ХОЗЛ) у стадії загострення, використовуючи різні режими антибактеріальних препаратів. У дослідженні брали участь 252 пацієнти із загостренням ХОЗЛ. Оцінювали стан пацієнта на 3-й, 5-й та 10-й дні лікування, а також через 30 днів після проведенного лікування. Усі пацієнти були поділені на три групи. Пацієнти 1-ї групи приймали комбінований препарат Амоксицилін–500 мг + Клавуланова кислота–125 мг три рази на добу впродовж 10 діб; пацієнти 2-ї групи приймали Ципрофлоксацин 500 мг два рази на добу впродовж 5 діб; пацієнти 3-ї групи приймали Роваміцин–3000000 МО два рази на добу впродовж 10 діб. Отримані результати були наступними: на 10-ту добу стабілізація стану (за трьома основними симптомами: кількість виділеного мокротиння, його гнійність, задишка) спостерігалась у 67 % пацієнтів, які отримували Ципрофлоксацин, та у 65 й 64 % пацієнтів, які отримували Амоксицилін/Клавуланову кислоту та Роваміцин відповідно. Проте швидкість настання ремісії відрізнялась у групах: вже на 3-тю добу лікування покращання стану спостерігалось у 20 % пацієнтів, які отримували Ципрофлоксацин, тоді як у тих, хто отримував Амоксицилін/Клавуланову кислоту та Роваміцин, – у 9,6 та 6,5 % відповідно. На 5-ту добу лікування ремісія спостерігалась у 49 % пацієнтів, які отримували Ципрофлоксацин, у 26,5 та у 30 % пацієнтів – із призначенням Амоксициліну/Клавуланової кислоти та Роваміцину. Отже, результати нашого дослідження показали, що приймання Ципрофлоксацину призводило до значно швидшого настання ремісії у хворих на ХОЗЛ у стадії загострення порівняно з тими пацієнтами, які отримували Амоксицилін/Клавуланову кислоту та Роваміцин.

Ключові слова: *загострення хронічного бронхіту, хронічне обструктивне захворювання легень, антибактеріальні режими.*

ОБОСТРЕНИЕ ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНИ ЛЕГКИХ И ЭФФЕКТИВНОСТЬ РАЗЛИЧНЫХ РЕЖИМОВ АНТИБАКТЕРИАЛЬНОЙ ТЕРАПИИ

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Целью данного исследования была сравнительная оценка эфективности различных антибактериальных препаратов у больных с хронической обструктивной болезнью легких (ХОБЛ) во время обострения. В исследовании принимали участие 252 пациента с обострением ХОБЛ. Оценка состояния пациентаов проводилась на 3-й, 5-й и 10-й дни лечения, а также через 30 дней после проведенного лечения. Все пациенты были разделены на 3 группы: пациенты 1-й группы принимали комбинированный препарат Амоксициллин–500 мг + Клавулановая кислота–125 мг три раза в день на протяжении 10 дней; пациенты 2-й группы – Ципрофлоксацин 500 мг два раза в день на протяжении 5 дней; пациенты 3-й группы – Ровамицин–3000000 МЕ два раза в день на протяжении 10 дней. На 10-й день лечения результаты были подобны в группах с учетом трех основных симптомов заболевания (количество выделяемой мокроты, ее гнойность, одышка). Так, стабилизация состояния наступила у 67 % пациентов, которые получали Ципрофлоксацин, у 65 % пациентов, которые получали Амоксициллин /Клавулановую кислоту, и у 64 % пациентов, которые получали Ровамицин. Однако скорость наступления ремиссии была различна в группах: уже на 3-й день лечения улучшение состояния наступило у 20 % пациентов, принимавших Ципрофлоксацин, у 9,6 % пациентов, которые принимали Амоксициллин /Клавулановую кислоту, и у 6,5 % пациентов, принимавших Ровамицин, соответственно улучшение состояния на 5-й день наступило у 49 % пациентов, получавших Ципрофлоксацин, у 26,5 и у 30 % больных, которые получали Амоксициллин /Клавулановую кислоту и Ровамицин. Следовательно, скорость наступления ремиссии ХОЗЛ во время обострения при использовании разных режимов антибиотикотерапии была значительно выше в группе пациентов, которые принимали Ципрофлоксацин.

Ключевые слова: *обострение хронического бронхита, хроническая обструктивная болезнь легких, антибактериальные режимы.*

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