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Effectiveness of differentiated regimens of antimicrobial chemotherapy in patients with acute exacerbation of chronic obstructive pulmonary disease without risk factors for pseudomonas aeruginosa infection

Key words: *COPD, infectious exacerbation, effectiveness of treatment, cost.*

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a major factor of disease progression, hospitalization of patients, worsening of quality of patients' lives, increase of mortality and financial expenses [1, 2].

A bacterial infection of bronchial tree is a leading cause of AECOPD [2].

Antibiotics, administered considering their pharmacokinetics and pharmacodynamics, as well as the evidences of clinical efficacy, provided by randomized clinical trials, are the mainstream of therapy in patients with AECOPD [7]. Nowadays, most of physicians prescribe antibiotics to these patients even in the absence of active respiratory tract infection [3, 5, 6]. Such an approach leads to ineffective use of antibiotics in more than 50 % of cases, increasing a spread of drug resistance, rate of adverse effects, prolonging the term of treatment and increasing its cost [7].

The aim of the study was to evaluate the clinical and economical effectiveness of differentiated regimens of antibacterial therapy of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) without risk factors for *P. aeruginosa* infection.

Materials and methods

Seventy eight AECOPD patients without risk factors for *P. aeruginosa* infection, were enrolled in the study. Below is a list of the risk factors:

- recent hospitalization;
- frequent (> 4 times per year) or recent (within last 3 months) use of antibiotics;
- severe COPD (FEV_1 < 30 %);
- use of oral steroids (> 10 mg of prednisolone daily for last 2 weeks).

All patients were randomized in 3 groups. Each subject received its individual number. Patients with numbers 1, 4, 7 etc. were allocated to group I; numbers 2, 5, 8 – group II, numbers 3, 6, 9 – group III. All patients signed an informed consent form.

The choice of antibiotic was done according to international and local recommendations [4, 8]. The efficacy of drug was assessed after 5 and 10 days after treatment had been started. In case where no response noted on day 5 of treatment antibiotic was changed to alternative one.

The patients of 1st group (26 subjects) received oral amoxicillin/clavulanate (Augmentin, GSK, Great Britain) 1000 mg twice daily, regardless of meals during 5–10 days (7,8 days mean).

The patients of 2nd group (26 subjects) received oral lefofloxacin (Tavanik, Aventis Pharma, France) 500 mg once daily regardless of meals during 5–10 days (7,4 days mean).

The patients of 3rd group (26 subjects) received i/m ertapenem (Invanz, MSD, USA) 1,0 once daily during 5–7 days (5,6 days mean).

There were no significant differences, which could cause bias between patients in terms of pharmacological therapy.

All patients were examined using physical (complaints, history, inspection), instrumental (radiography, ECG, spirometry) and laboratory (blood count, chemistry, urinalysis) tests.

All study data were analyzed using the standard methods of statistics. Method of «cost minimization» was used for pharmacoeconomical analysis. This method was chosen because of the absence of meaningful differences in efficacy of studied antibiotics and the rates of adverse events between groups.

The study was performed under the government financial support.

Results

Clinical and laboratory characteristics of patients are presented in Table 1.

These data confirm a complete compatibility of comparison groups. Concomitant diseases (chronic sinusitis, chronic cholecystitis, coronary heart disease, arterial hypertension, asthma) were diagnosed in all patients.

The similar positive results of treatment were achieved in all groups. Initial improvement was noted in a majority of patients on 5th day. Sub-febrile body temperature was registered in (15,4 ± 7,1) % of patients in group I and (11,5 ± 6,3) % of patients in group II. Moreover, in most cases (85,4 % in group I, 88,5 % in group II, and 96,2 % in group III) the purulence of sputum have decreased.

At the same time, on 5th day of treatment in 4 (15,4 %) patients of group I, III (11,5 %) patients of group II and I (3,8 %) patient from group III the body temperature stayed febrile along with increase of cough and purulent sputum discharge, and leukocytosis. Such cases were considered treatment failure and study antibiotic was switched to alternative one. In groups I and II ertapenem 1,0 once daily i/m for 5 days was used as a second-line therapy. In group III oral levofloxacin (Tavanik, France) 500 mg once daily for 5 days was administered as an alternative antibiotic.

After completion of treatment a sub-febrile body temperature was only noted in (7,7 ± 5,2) % of group I patients and (3,8 ± 3,7) % of group II patients (Tab. 2). An intensity of dyspnea decreased in all patients. A reduction of cough, sputum discharge and lung rales was less evident, nevertheless the partial resolution of symptoms we observed almost in all patients.

A clinical improved was accompanied by a reduction of white blood cells count to the level of (5,1 ± 1,4) × 10^9/l (group 1), (6,3 ± 1,1) × 10^9/l (group 2) and (5,5 ± 1,0) × 10^9/l (group III) (Tab. 2). The same trend was revealed for ESR as well. The value of this index decreased to (6,1 ± 0,5) mm/h in group I and to (7,2 ± 1,2) and (5,0 ± 0,7) mm/h in groups II and III ($p < 0,05$).

There were no significant differences in adverse events rates between groups I, II and III: (23,1 ± 8,3), (19,2 ± 7,7) and (15,4 ± 7,1) %, respectively ($p > 0,05$). All adverse reactions were mild, and didn't require and interruption of therapy. An elevation of transaminases, diarrhea and stomach pain were observed most frequently.

As confirmed by both clinical and laboratory data the rate of improvement was (84,6 ± 7,1) % in 1st group, (88,5 ± 6,3) % – in 2nd group and (96,2 ± 3,7) % – in 3rd group of study patients ($p > 0,05$).

A pharmacoeconomical analysis was conducted in per protocol study population and those patients, who stopped study therapy because of treatment failure. In group I patients the cost distribution was as following: cost of antibiotic therapy – 73, 1 %, cost of medicinal therapy was 83,8 %, cost of antibiotic – 15,5 % of total cost. The cost of study antibiotic was 21,2 % of antibiotic therapy and 18,5 % of medicinal therapy. The cost of diagnostic tests and consultancy cost were not substantial, accounting only for 16,2 % of total cost of treatment.

Table 1

Clinical characteristics of patients before treatment

Index	Group		
	I (n = 26)	II (n = 26)	III (n = 26)
Age, years	61,4 ± 4,9	66,3 ± 5,7	60,8 ± 5,0
Body temperature < 37 °C, %	65,4 ± 9,3	53,8 ± 9,8	50,0 ± 9,8
Body temperature > 37 °C ≤ 38 °C, % of patients	34,6 ± 9,3	46,2 ± 9,8	50,0 ± 9,8
Dyspnea at exercise, %	15,4 ± 7,1	23,1 ± 8,3	19,2 ± 7,7
Dyspnea at minor exercise, %	76,9 ± 7,1	73,1 ± 8,7	69,3 ± 9,0
Dyspnea at rest, %	7,7 ± 5,2	3,8 ± 3,7	11,5 ± 6,3
Cough, %	100	100	100
Sputum, % of patients	92,3 ± 5,2	96,2 ± 3,7	100
Rales, % of patients	88,5 ± 6,3	92,3 ± 5,2	96,2 ± 3,7
WBC, × 10^9/l	10,3 ± 1,1	9,7 ± 0,6	9,9 ± 1,2
ESR, mm/h	21,3 ± 1,8	19,4 ± 1,6	18,3 ± 1,3

Table 2

Clinical characteristics of patients after completion of treatment

Index	Group		
	I (n = 26)	II (n = 26)	III (n = 26)
Body temperature < 37 °C, %	92,3 ± 5,2	96,3 ± 3,7	100
Body temperature > 37 °C ≤ 38 °C, % of patients	7,7 ± 5,2	3,8 ± 3,7	0
Dyspnea at exercise, %	76,9 ± 8,3	69,2 ± 9,1	65,4 ± 9,3
Dyspnea at minor exercise, %	23,1 ± 8,3	30,8 ± 9,1	34,6 ± 9,3
Cough, %	100	100	96,2 ± 3,7
Sputum, % of patients	84,6 ± 7,1	96,2 ± 3,7	80,8 ± 7,7
Rales, % of patients	76,9 ± 8,3	84,6 ± 7,1	69,2 ± 9,1
WBC, $\times 10^9$/l	5,1 ± 1,4	6,3 ± 1,1	5,5 ± 1,0
ESR, mm/h	6,1 ± 1,3	7,2 ± 1,2	5,0 ± 0,7

Note: there were no statistically significant differences between groups (p > 0,05).

Table 3

Treatment cost structure per one patients with AECOPD, UAH

Type of cost	Group		
	I (n = 26)	II (n = 26)	III (n = 26)
Cost of antibiotic	99,6 ± 5,2	398,7 ± 7,5*	2877,0 ± 12,3*#+
Cost of antibiotic delivery	–	–	0,9 ± 0,7
Cost of personnel work	–	–	1,6 ± 1,1
Cost of antibiotic therapy	468,8 ± 7,0	675,6 ± 8,2*	3246,7 ± 15,6*#+
Cost of medicines, other than antibiotics	68,9 ± 6,6	73,5 ± 7,4	72,5 ± 7,1
Cost of diagnostic tests	84,4 ± 6,8	93,7 ± 6,3	80,9 ± 6,5
Cost of consultations	19,4 ± 5,2	22,6 ± 4,6	27,3 ± 4,7
Total cost of treatment	641,5 ± 8,0	865,4 ± 8,3*	3427,4 ± 16,1*#+

Notes: * – (p< 0,05) between groups I and II; # – (p< 0,05) between groups I and III; + – (p< 0,05) between groups II and III.

In groups II and III the cost of antibiotic therapy also dominated (78,1 and 94,7 %, respectively). The odds of medicinal therapy were 86,6 and 96,8 %; treatment with study antibiotic – 46,1 and 83,9 %, respectively. The costs of diagnostic tests and consultations were 13,4 % and 3,2 in these groups, respectively.

It is necessary to put a stress that the lowest cost of antibiotic treatment was registered in 1st group. The cost of treatment in group II was significantly lower than in group II. There were no significant differences in other costs between groups.

Conclusion

The use of empiric therapy with either amoxicillin/clavulanate, levofloxacin and ertapenem in AECOPD patients without risk factors for *P. aeruginosa* infection was equally effective and safe. Pharmacoeconomically proved most efficient antibiotic of choice in current patients was oral amoxicillin/clavulanate. A fluoroquinolone or ertapenem could be used as a second-line treatment option.

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ИССЛЕДОВАНИЕ ЭФФЕКТИВНОСТИ ДИФФЕРЕНЦИРОВАННЫХ СХЕМ АНТИМИКРОБНОЙ ХИМИОТЕРАПИИ БОЛЬНЫХ С ИНФЕКЦИОННЫМ ОБОСТРЕНИЕМ ХОЗЛ БЕЗ ФАКТОРОВ РИСКА СИНЕГНОЙНОЙ ИНФЕКЦИИ

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Резюме

Цель исследования. *Оценка клинической и экономической эффективности дифференцированных схем антибактериальной терапии у больных с инфекционным обострением хронического обструктивного заболевания легких (ХОЗЛ) без факторов риска синегнойной инфекции.*

Материалы и методы. *Обследовано 78 больных с инфекционным обострением ХОЗЛ без наличия у них факторов риска инфекции, вызванной синегнойной палочкой. Пациентов рандомизировали в 3 подгруппы. Пациенты I, II и III подгрупп получали лечение амоксициллин / клавуланатом в дозе 1000 мг два раза в сутки перорально, левофлоксацином в дозе 500 мг один раз в сутки перорально и эртапенемом в дозе 1,0 г один раз в сутки внутримышечно соответственно. Всем больным проводили комплексное клиническое, лабораторное и функциональное обследование.*

Результаты. *Анализ динамики клинико-лабораторных данных свидетельствует о том, что проведенная антибактериальная монотерапия способствовала достижению одинаковых положительных результатов во всех подгруппах: у (84,6 ± 7,1) % больных I подгруппы, у (88,5 ± 6,3) % больных II подгруппы и у (96,2 ± 3,7) % больных III подгруппы (p > 0,05). Стоимость терапии пациентов I подгруппы была достоверно ниже стоимости терапии во II и III подгруппах.*

Выводы. *Применение эмпирической терапии с использованием амоксициллина / клавуланата, левофлоксацина и эртапенема у больных с инфекционным обострением ХОЗЛ без факторов риска синегнойной инфекции является одинаково высокоэффективным и безопасным.*

Ключевые слова: *ХОЗЛ, инфекционное обострение, эффективность лечения, стоимость.*

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EFFECTIVENESS OF DIFFERENTIATED REGIMENS OF ANTIMICROBIAL CHEMOTHERAPY IN PATIENTS WITH ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE WITHOUT RISK FACTORS FOR PSEUDOMONAS AERUGINOSA INFECTION

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Abstract

The aim of the study *was to evaluate the clinical and economical effectiveness of differentiated regimens of antibacterial therapy of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) without risk factors for P. aeruginosa infection.*

Materials and methods. *78 patients with AECOPD were randomized in 3 groups to receive treatment with either oral amoxicillin / clavulanate 1000 mg twice daily, or lefofloxacin 500 mg once daily, or i/m ertapenem 1,0 once daily. All patients were examined using physical and laboratory tests.*

Results. *The similar positive results of treatment were achieved in all groups. The rate of clinical and laboratory improvement was (84,6 ± 7,1) % in 1st group, (88,5 ± 6,3) % – in 2nd group and (96,2 ± 3,7) % – in 3rd group of study patients. The lowest cost of treatment was registered in 1st group.*

Conclusion. *The use of empiric therapy with either amoxicillin / clavulanate, levofloxacin and ertapenem in AECOPD patients without risk factors for P. aeruginosa infection was equally effective and safe.*

Key words: *COPD, infectious exacerbation, effectiveness of treatment, cost.*

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