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Acute exacerbation of chronic obstructive pulmonary disease, caused by viruses: the need of combined anti-infective chemotherapy

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The *aim* of the study was to evaluate the effectiveness of combined antibacterial and anti-viral therapy of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), caused by viruses.

Materials and Methods: 56 patients with AECOPD, triggered by acute respiratory viral infection (ARI) were enrolled. All patients were administered amoxicillin/clavulanate 1000 mg twice daily plus vitaglutam 90 mg once daily (1st group) or amoxicillin/clavulanate 1000 mg twice daily (2nd group). All patients were examined using physical and laboratory tests. Biological samples of all patients were also tested in order to identify viral and bacterial pathogens.

Results: In patients of 1st group we observed shorter use of antibiotic, lower rate of infectious complications and faster clinical and laboratory recovery. The data of pharmacoeconomical analysis indicated that the cost of antimicrobial therapy was lower in the 1st group as well.

Conclusion: A combined anti-infective therapy, enhanced by anti-viral medication vitaglutam, could significantly improve the outcomes of treatment of patients with AECOPD, caused by viruses.

Keyword: Acute Exacerbation, Viruses, COPD, Vitaglutam.

1. Introduction

Current standards of management of patients with acute exacerbation of chronic obstructive pulmonary disease (AE COPD) recommend the use of antibacterial chemotherapy in following indications:

– Exacerbation of type 1;
– Exacerbation of type 2;
– Any exacerbation of COPD, requiring non-invasive or invasive ventilation [1, 2, 3].

The choice of antibiotic in treatment of patients with AE COPD should be based on bacteriological and/or virological examination, consider pharmacokinetics and pharmacodynamics of the compounds and the efficacy data, produced in randomized controlled trials [4].

The data of latest clinical trials have confirmed the role of viruses as a trigger factors and as important pathogens in AE COPD [5, 6].

According to literature data about 50–60 % of all cases of AE COPD are caused by bacterial, and 30–40 % — by viral pathogens [7]. Moreover, a mixed etiology is found in a big portion of these cases [8]. This consideration makes a study of combined antibacterial and antiviral therapy effectiveness an important task of modern medical science.

Current study was conducted in order to evaluate the clinical and economical effectiveness of combined antibacterial and anti-viral treatment of patients with, caused by viruses.

2. Materials and Method

We examined 56 COPD patients in whom an AE was diagnosed on the background of acute respiratory viral infection (ARI). The patients were randomly distributed into two groups. The patients of 1st group (28 patients) were treated with a combination of antibiotic with antiviral medication; the patients of 2nd group (control) — with antibiotic only.

In both groups there were no risk factors of *P. aeruginosa* infection: no recent hospitalization or recent use of antibiotics, FEV_1 > 30 % predicted, no systemic steroids). The patients of both groups were treated with empirically administered antibiotic — amoxicillin/clavulanate (Augmentin TM, by GSK, UK) 1000 mg twice daily irrespectively of meals. The patients of 1st group were additionally administered with vitaglutam from the first day of therapy (Ingavirin TM, Valenta, Russia) 90 mg once daily with no respect of food intake for 5–7 days (in average 5.3 days).

In all cases the exacerbation manifested from AR) with such the symptoms as headache, running nose, sore throat, malaise, arthralgia, photophobia, weakness and fever (37–39 ° C). Clinical examination revealed the signs of rhinitis (85,7 % of patients), palate and throat hyperemia (89,3 % of patients) and conjunctive membrane of eye hyperemia (78,6 % of patients). In patents of both groups almost simultaneously (in (5,2 ± 0,4) and (6,1 ± 0,7) days, respectively) the diagnosis of AE COPD was established and the patients were hospitalized.

Table 1: Clinical symptoms in patients with AE COPD trigerred by viruses before start of antimicrobial therapy

Symptom	Group	
	1st (n = 28)	2nd (n = 28)
Age, years	61,3 ± 3,4	64,1 ± 3,5
Sex:		
male, %	78,6 ± 7,8	82,1 ± 7,2
female, %	21,4 ± 7,8	17,9 ± 7,2
Term of AE COPD diagnosis after beginning of ARI, days	5,2 ± 0,4	6,1 ± 0,7
Body temperature:		
≤ 37 °C, %	7,1 ± 4,8	10,7 ± 5,8
> 37 °C ≤ 38 °C, %	71,4 ± 8,5	64,3 ± 9,1
> 38 °C, %	21,5 ± 7,8	25,0 ± 8,3
Dyspnea:		
Regular exercise, %;	10,7 ± 5,8	17,8 ± 7,2
Mild exercise, %;	67,9 ± 8,8	67,9 ± 8,8
At rest, %;	21,4 ± 7,8	14,3 ± 6,6
Cough, %	100	100
Sputum:		
mucous-purulent, % patients	53,8 ± 9,4	60,7 ± 9,2
purulent, % patients	46,2 ± 9,4	39,3 ± 9,2
Rhonchi, % patients	100	100
Blood white blood cells count, 10^9 /l	10,8 ± 1,2	13,0 ± 2,4
ESR, mm/h	30,2 ± 3,6	27,8 ± 2,6

Note: No statistically significant difference between groups (p > 0,05).

Clinical and laboratory characteristics of patients are presented in Table 1. Mean age of patients of 1st group was (61,3 ± 3,4) years, (78,6 ± 7,8) % were males. The term of onset of AE COPD after beginning of ARI was (5,2 ± 0,4) days. In (7,1 ± 4,8) % of patients a body temperature was < 37

°C, in (71,4 ± 8,5) % of patients — < 38 °C and in (21,5 ± 7,8) % of patients — above 38 °C.
Mean age of patients of 2nd group was (64,1 ± 3,5) years, 82,1 % were males. The term of onset of AE COPD after beginning of ARI was (6,1 ± 0,7) days. In (10,7 ± 5,8) % of patients a body temperature was < 37 °C, in (64,3 ± 9,1) % of patients — < 38 °C and in (25,0 ± 8,3) % of patients — above 38 °C.

These data confirm a complete compatibility of comparison groups.

The samples of sputum and nasal discharge were tested soon after hospitalization of the patients for detection of causing pathogen. Sputum bacterioscopy was performed in all patients. The positive smears were detected in 26 (92,9 %) cases in group 1 and in 24 (85,7%) cases in group 2. Smear-positive samples were further cultured, allowing to isolate bacterial strains in 21 (70,7 %) cases in group 1 and in 19 (68,8 %) cases in group 2. It should be noted, that in 3 patients of group 1 and in 2 patients of 2nd group two pathogens were isolated.

Pharmaco-economic analyses was done in all patients, diagnosed with AE COPD of mixed etiology, enrolled into the study and completed treatment per protocol and in those who interrupted treatment due to treatment failure. The method of cost/efficiency was used in this evaluation. The reasons why this method had been chosen were the presence of statistically significant differences in clinical efficacy between the compared therapies and the lack of differences in safety and tolerability.

3. Results and Discussion

The most commonly isolated microorganism in both groups was *H. influenzae* (45,8 % and 52,4 % cases in group 1 and 2, respectively), *S. pneumoniae* (20,8 % and 19,0 % cases) and *Enterobacteriaceae spp.* (25,0 % and 23,8 % cases). Other bacterial were detected much less frequently — in about 5 % of all cases (Fig. 1, 2).

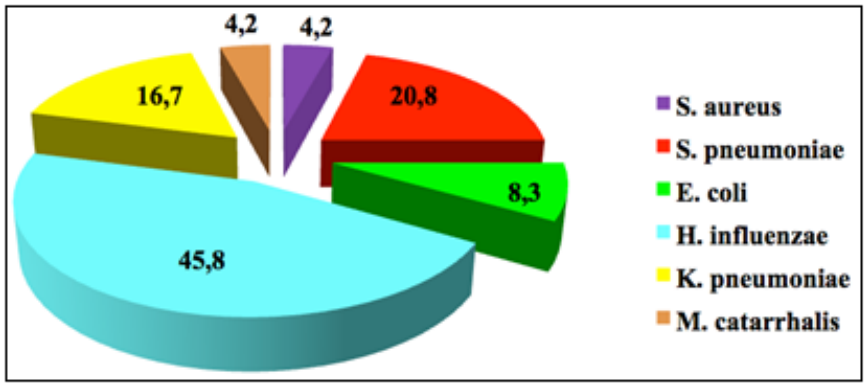

Fig 1: Distribution of bacterial pathogens, isolated in group 1, %

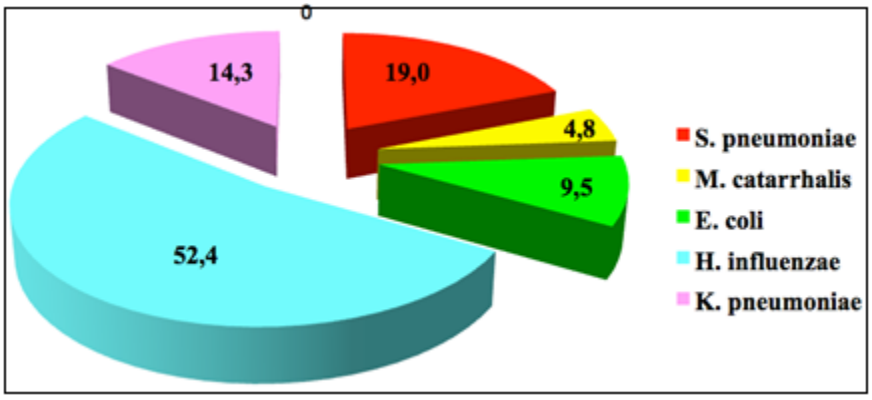

Fig 2: Distribution of bacterial pathogens, isolated in group 2, %

Viruses were identified by means of polymerase chain reaction (PCR). In 22 (78,6 %) patients of 1st group 25 strains of viruses were revealed. In 19 (86,4 %) patients there was detected 1 strain, in 3 (13,6 %) — 2 strains of viruses. In patients of 1st group the most frequent pathogens were rhinoviruses (48,0 %), adenoviruses (16,0 %) and bocaviruses (12,0 %). Other viruses were detected in 8 % of patients (Fig. 3).

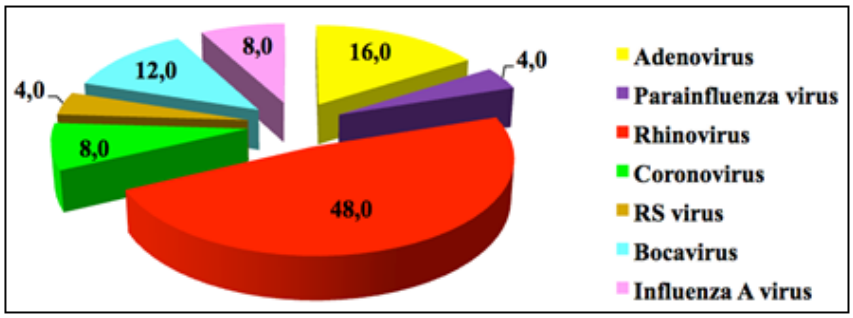

Fig 3: Distribution of viruses, isolated in group 1, %

In 20 (71,4 %) patients of 2nd group 24 strains of viruses were revealed. In 16 (57,1 %) patients there was detected 1 strain, in 4 (28,3 %) — 2 strains of viruses. In patients of 2nd group the most frequent pathogens were rhinoviruses (45,8 %), adenoviruses and influenza A virus (12,5 % each). Other viruses were detected in 9 % of patients (Fig. 4).

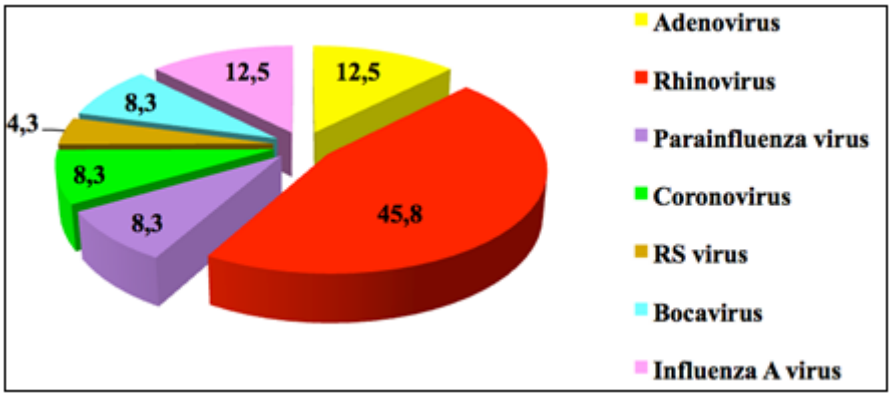

Fig 4: Distribution of viruses, isolated in group 2, %

Since in 2 patients from group 1 and 3 patients from group 2 the influenza A virus was detected, further virology tests were conducted, which establishe a sub-type of virus — A (H_3N_2).

An infectious complications, affecting the course of disease, were registered in 4 patients of group 1 and 9 patients of group 2.

Thus in patients of 1st group an infectious complications were observed significantly more rarely, than in 2nd group ((14,3 ± 2,6) % vs (32,1 ± 2,8%) % respectively, $p < 0,05$).

An improvement of patients' condition was observed on 5th day of treatment (a decrease of body temperature, clearance of sputum, disappearance of rhonchi). Nevertheless, in 2 (7,1 %) patients of 1st group and in 5 (17,9 %) patients of 2nd group the fever persisted and was associated with an increase of cough, purulent sputum discharge and peripheral blood leukocytosis. Such cases were considered a treatment failure. A therapy was switched to an alternative antibiotic — ertapenem (Invanz TM, MSD, USA) 1,0 i/v once daily for 5–7 days (in average 5,6 days).

After treatment a fever was only observed in (7,1 ± 4,8) % of 1st and (28,6 ± 9,2) % of 2nd group

patients ($p < 0,05$). In majority of patients the dyspnea decreased after treatment. A dyspnea, caused by regular exercise was significantly more frequent in patients from 1st group. The cough remained in all patients, whereas the purulent sputum cleared in more patients from 1st group, as well as rhonchi disappeared, which was statistically significant.

A clinical improvement correlated with blood count positive changes. A statistically significant reduction of white blood cells count ($p < 0,05$) was observed after treatment in both groups (Table 2). Same trend was noted for the ESR, reaching (7,1 ± 1,6) mm/h in the 1st group and (10,2 ± 2,1) mm/h — in the 2nd ($p < 0,05$).

Table 2: Clinical symptoms in patients with AE COPD of mixed etiology after antimicrobial therapy was initiated

Symptom	Group	
	1st (n = 28)	2nd (n = 28)
Body temperature:		
≤ 37 °C, %	7,1 ± 4,8	10,7 ± 5,8
> 37 °C ≤ 38 °C, %	71,4 ± 8,5	64,3 ± 9,1
> 38 °C, %	21,5 ± 7,8	25,0 ± 8,3
Dyspnea:		
Regular exercise, %;	42,9 ± 9,3	17,8 ± 7,2*
Mild exercise, %;	57,1 ± 9,3	78,6 ± 7,7
At rest, %;	0	3,6 ± 3,5
Cough, %	100	100
Sputum:		
mucous-purulent, % patients	82,2 ± 7,2	57,1 ± 9,3*
purulent, % patients	17,8 ± 7,2	42,9 ± 9,2*
Rhonchi, % patients	21,4 ± 7,7	57,1 ± 9,3*
Blood white blood cells count, 10^9 /l	4,6 ± 1,5	7,1 ± 1,6
ESR, mm/h	8,3 ± 2,3	10,2 ± 2,1

Note: * —statistically significant differences between groups ($p > 0,05$).

The analysis of safety and tolerability revealed no differences between groups in the rates of adverse events (AE): (28,6 ± 9,2) % in 1st group and (21,4 ± 7,7) % — in the 2nd ($p > 0,05$). All registered AEs were mild and didn't require modification of treatment. Temporary elevation of ALT, diarrhea, stomach pain, nausea were the most frequently observed AEs in patients of both groups.

The mean duration of antibiotic therapy in the 1st group was significantly shorter than in the 2nd — (9,2 ± 1,3) vs (12,9 ± 1,1) days, respectively ($p < 0,05$).

The results demonstrated that the improvement was registered in (92,9 ± 4,8) % of patients of the 1st group and in (71,4 ± 9,2) % of patients of the 2nd group ($p < 0,05$).

In order to evaluate the economical benefits of combined therapy a pharmaco-economic analysis was conducted. The results demonstrated that regardless of additional expenses, associated with the cost of vitaglutam, the total cost of antimicrobial therapy in the 1st group was statistically lower than in the 2nd (816,7 ± 9,8 vs 1166,9 ± 11,3 UAH, respectively, ($p < 0,05$)). This was mainly due to shorter duration of treatment, lower rate of infectious complications and faster improvement of the patients.

A pharmaco-economic analysis clearly proved an advantage of therapy in patients of 1st group with lower expences due to shorter course of treatment in comparison to the 2nd group. At the same time,

the other expenses, associated with consultancy and diagnostic tests didn't significantly differ between groups. These findings confirmed the overall better cost/efficiency ratio in favor to the therapy in the 1st group of AE COPD patients.

4. Conclusion

In patients with AE COPD, triggered by viruses, an empiric antibiotic therapy, enhanced by vitaglutam, significantly decreased the rate of infectious complications, reduced the duration of antibiotic use, accelerated improvement of patients and increase the overall effectiveness of treatment. The use of vitaglutam was justified by the data of pharmaco-economic analysis.

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