INTRODUCTION

According to modern concepts, the diagnosis of acute rhinosinusitis (ARS) includes three separate nosological units: viral, post-viral and bacterial rhinosinusitis [1]. It is well known that adults suffer from two to five episodes of acute viral rhinosinusitis (AVRS, or cold) a year, and the prevalence of acute post-viral rhinosinusitis (APVRS) equals to 18% (17-21%) [2,3]. The acute bacterial rhinosinusitis (ABRS) morbidity rate is established at the level of 0.5-2% of all viral sinus infections [4,5].

The typical causative agents of AVRS in adults are rhinoviruses and coronavirus which constitute around 50% of all cases [6,7]. The typical representatives of ABRS are S. pneumoniae, Haemophilus influenza and M. catarrhalis, and less frequently - S. aureus. There are also other types of streptococci and anaerobic bacteria [8,9]. It is reasonable to assume that ABRS most likely is the stage of evolution of the post-viral one as it is usually followed by ABRS [1,4]. The saprophytic bacteria in APVRS such as streptococci, staphylococci and gram-negative bacteria produce toxins against immune system, leucocytes or epithelial cells creating a kind of background for its transformation into ABRS [8].

Many studies have proved that the epithelium of nasal cavity actively initiates innate immune responses and also modulates adaptive immunity against viruses [10,11,12]. Epithelial cells involves their own immune responses and actively prevent the respiratory passages are damaged by pathogens releasing antiviral and antimicrobial agents and mucus to stop the transmission of pathogens into respiratory tracts [13-15]. The also express and secrete various cytokines and chemokines as well as immunoglobulines to stimulate immune reactions against intervention of pathogens into respiratory tracts [16,17]. It is secretory immunoglobulin A (sIgA) that plays an important role in implementation of local immunity which has ability to neutralize viruses. Secretory system IgA also affects the processes of absorption and adhesion of microbial cells to the epithelium of mucous membranes. In combination with lysozyme and complement, sIgA has a strong bactericidal and antiviral activity [18].

In routine clinical practice it is rather difficult to establish the difference between APVRS and ABRS that is complicated to identify the adequate indications for antibacterial therapy [1,19]. This results in prescribing antibiotics in ARS 4-9 times more frequently than it is recommended in clinical guidelines [20]. Present strategy which is aimed to reduce the number of irrational antibiotic prescriptions is delayed prescription [21]. The important precondition for successful implementation of technique of delayed prescription of antibiotics is the treatment of APVRS regulated by the guidance that includes irrigation therapy and topical corticosteroids [1,22].

Within the strategy of delayed prescription of antibiotics
in acute rhinosinusitis, the use of bacteriophages might be interesting as according to the studies they are able to influence the number of pathologic processes in ENT organs [23]. Phages, unlike antibiotics, can be used not only for treatment but also for prevention of infectious diseases [24].

THE AIM
To evaluate the efficiency of additional prescription of bacteriophage through evaluation of a clinical picture, microbiological and immunological indices in patients with acute rhinosinusitis within the technique of delayed prescription of antibiotics.

MATERIALS AND METHODS
155 outpatients with clinical criteria of APVRS participated in the research [1,22]. The research was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethical committee. Each participant gave informed consent for the trial. There were included 24 (30,0%) of men and 56 (70,0%) of women into the intervention group (n – 80), 20 (26,7%) of men and 55 (73,3 %) of women into the control group (n - 75). The average age of patients of the intervention group was 36,24 years old, and 41,29 years old of the control group. All the patients received the irrigation therapy with isotonic solution of sea water 4 times a day and mometasone furoate of accumulated dose of 200 mg since the first day of treatment. The intervention group (n - 80) was additionally prescribed the polyvalent bacteriophage endonasally, in drops of 2-10 ml 3 times a day since the first day of treatment. The medication is registered in Ukraine.

The supervision of patients consisted of four visits which lasted for 10 days. On the V1 (day 0) the participants were engaged into the trial and prescribed treatment. On the V2 (day 5±1) the state and effectiveness of treatment were evaluated. Nasal discharge, post-nasal drip on the back of the throat, nasal congestion, headache, facial pain were assessed during each visit under the scale MSS (Main Symptoms Severity score).

The design of the study provided that there was an intake of material from the middle nasal meatus under endoscopic control for bacteriological research on the V2, aimed to evaluate the qualitative composition of microflora. On the V1 и V4 there was an intake of nasal swabs and blood serum for immunological test (slgA and serum IgA), whose concentration was determined by solid-phase enzyme-linked immunoabsorbent assay. The key factors for effectiveness were as follows: the reduction in symptom severity assessed during each visit under the scale MSS in comparison with the 1st visit, frequency of prescription of antibiotics. The secondary criteria: changes of microbiological and immunological indices.

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Data processing. To analyse the homogeneity of groups, the methods of descriptive statistics (for quantitative indices - n, arithmetic mean, median, standard deviation, lowest value and highest value; for qualitative indices– frequency and percentage %) were used. For quantitative indices, the verification under the criteria of Shapiro-Wilk test and Mann-Whitney test was performed. The level of value for criteria of Shapiro-Wilk test was accepted to be 0,01, and for other criteria - 0,05.

RESULTS
The relative dynamic regression (%) of APVRS symptoms is presented in Figure 1.

While evaluating the typical symptoms of APVRS, both groups demonstrated indices compared as for their significance on the V1. In the course of treatment the regression of symptoms was noticed on the V2, V3 and practically to the complete regression on the V4 in the intervention and control groups. The data of comparative analysis of the symptom dynamics between the groups are presented in Table I.

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**Fig. 1. Relative dynamic regression (%) of APVRS symptoms**

![Graph showing relative dynamic regression.]
As for the dynamics of significance of main symptoms: nasal discharge, nasal congestion, post-nasal drip, the groups differed statistically on the V2 (p<0.05). Difference in the dynamics of additional symptoms: headache and facial pain were not reliable enough (p>0.05).

According to the design of study, the complex evaluation of a patient's state was performed on the V2 (the third day of treatment) and the decision whether it was necessary to prescribe antibacterial therapy was taken. In Table II the data as for delayed prescription of antibiotics are presented.
31 of 80 patients, which drew up 38.8%, of the intervention group needed the prescription of antibiotics. 44 of 75 patients, which drew up 58.7%, of the control group were prescribed antibiotics. The data comparison according to χ² criteria has shown that there is a significant difference in prescription of antibiotics between the patients of the intervention group and the control one (р=0,0204).

The analysis of nasal microflora composition in the groups by descriptive statistics methods is presented in Figure 2.

The gram-positive microorganisms prevailed among the cultures which were separated. Staphylococcus aureus could be found by 36.6% less frequent in the intervention group than in the control group, Streptococcus viridans– by 8.8% and Streptococcus pneumonia - by 3.5%. Among all the gram-negative microorganisms, Moraxella catarrhalis could be found by 8.8% less frequent in the intervention group than in the control group, Haemophilus influenzae– correspondingly by 4.7%.

We analysed the influence on the frequency of antibiotic prescription depending on the major pathogens of ABRS (Table III).

The outcomes presented show that Staphylococcus aureus has the greatest influence on the frequency of antibiotic prescription in the intervention group, whereas in the control group the presence of three types of microflora: Staphylococcus aureus, Haemophilus influenzae and Streptococcus pneumoniae.

We performed the comparative analysis of the changes in the levels of IgA and sIgA between the groups in the course of treatment (Table IV).

Based on the results of evaluation (Table IV) the following conclusion can be made: the groups did not differ in respect of initial state (V1) as for IgA and sIgA levels, but on the 10 day (V4) there are significant differences between the groups considering the indices mentioned above.

The assessment of acceptability showed that the treatment was acceptable in all cases. No patients had the side-effects in the course of treatment.

DISCUSSION

The completed study has demonstrated that the use of polyvalent bacteriophage in addition to the standard therapy for APVRS as a part of the technique of delayed prescription of antibiotics showed the effectiveness which was proved. The patients in the intervention group in comparison with the control group demonstrated clinically significant, reliable reduction in symptom severity by the third (V2) day of treatment (р<0.05). There was observed a “therapeutic advantage” in clinical outcomes which made it possible to assess the disease dynamics as a “positive” one and take an appropriate decision about antibiotic therapy tactics. The number of prescriptions of antibiotics reduced by 20% (р<0.005). The reduction in the number of antibiotic prescriptions correlates with normalization of species composition of bacterial flora. Staphylococcus

Table II. Comparison of the groups following the prescription of antibiotics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>N (%)</th>
<th>χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of antibiotic prescriptions</td>
<td>Intervention (n 80)</td>
<td>31 (38,8)</td>
<td>5,377</td>
<td>0,0204</td>
</tr>
<tr>
<td></td>
<td>Control (n 75)</td>
<td>44 (58,7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Conclusion was made with significance level equal to 0.05

Table III. Assessment of the significance of influence of microflora on the frequency of antibiotic prescription.

<table>
<thead>
<tr>
<th>Influential factors</th>
<th>Value</th>
<th>Standard error</th>
<th>Wald test statistics</th>
<th>Number of degrees of freedom</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staph. aureus</td>
<td>-0.351</td>
<td>0.809</td>
<td>0.188</td>
<td>1</td>
<td>0.665*</td>
</tr>
<tr>
<td>Haem. influenz.</td>
<td>3.569</td>
<td>1.140</td>
<td>9.800</td>
<td>1</td>
<td>0.002</td>
</tr>
<tr>
<td>Mor. catarrhalis</td>
<td>3.009</td>
<td>0.884</td>
<td>11.583</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Strep. pneumon.</td>
<td>2.371</td>
<td>0.786</td>
<td>9.093</td>
<td>1</td>
<td>0.003</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staph. aureus</td>
<td>-0.257</td>
<td>0.517</td>
<td>0.246</td>
<td>1</td>
<td>0.620*</td>
</tr>
<tr>
<td>Haem. influenz.</td>
<td>-0.417</td>
<td>0.683</td>
<td>0.372</td>
<td>1</td>
<td>0.542*</td>
</tr>
<tr>
<td>Mor. catarrhalis</td>
<td>1.212</td>
<td>0.730</td>
<td>2.757</td>
<td>1</td>
<td>0.097</td>
</tr>
<tr>
<td>Strep. pneumon.</td>
<td>-0.696</td>
<td>0.688</td>
<td>1.025</td>
<td>1</td>
<td>0.311*</td>
</tr>
</tbody>
</table>

* statistically significant difference can be seen
aureus has the greatest influence on the frequency of antibacterial prescription in the intervention group whereas in the control group the presence of three types of microflora: Staphylococcus aureus, Haemophilus influenzae and Streptococcus pneumonia (p<0.005). The positive outcomes of clinical symptomatology and microbiological pattern correlates with improvement of immunological indices. In 10 days of treatment the reliable higher levels of IgA and sIgA were observed in patients of the intervention group in comparison with the control group (p<0.005). These differences are connected with additional prescription of polyvalent bacteriophage as no other medications were prescribed. The results obtained reflect few data concerning the effectiveness of bacteriophage [23,24]. The proven effectiveness of APVRS treatment with bacteriophage will allow to apply the technique of delayed prescription of antibiotics extensively and greatly reduce the number of irrational prescriptions of antibacterial medications on the first visit of a patient.

CONCLUSIONS
1. The use of polyvalent bacteriophage in addition to the standard therapy for the treatment of APVRS provides the significant clinical effect in the early days of treatment.
2. The positive outcomes of clinical symptomatology correlates with normalization of species composition of resident flora in the nasal cavity and improvement of IgA and sIgA levels.
3. The clinical, microbiological and immunological effects can reduce the number of prescriptions of antibacterial preparations by 20%.
4. The inclusion of the preparation into the treatment regimen can be recommended in patients with APVRS within the technique of delayed prescription of antibiotics.

REFERENCES


The study was conducted as a part of the research scientific paper «Clinical, ex-ray, laboratory parallels to optimize the technique of diagnostic and treatment in inflammatory diseases of respiratory tracts and ear». State registration number 0121U109999.

**ORCID and contributionship:**
Vasyl I. Popovych: 0000-0002-2898-8474 A, F
Ivanna V. Koshel: 0000-0002-5466-4537 R, E, D
Mahmoud J. Al Hariri: 0000-0002-8669-7026 B, C, D, F

**Conflict of interest:**
The Authors declare no conflict of interest.

**CORRESPONDING AUTHOR**
Vasyl I. Popovych
Ivano-Frankivsk National Medical University
2 Halijtska St., 76018 Ivano-Frankivsk, Ukraine
tel: +38 (067) 344-8577
e-mail: popovychvasyl@gmail.com

**Received:** 11.11.2020
**Accepted:** 27.04.2021

A - Work concept and design,
B – Data collection and analysis,
C – Responsibility for statistical analysis,
D – Writing the article, E – Critical review, F – Final approval of the article