ORIGINAL ARTICLE

CLINICAL AND LABORATORY JUSTIFICATION FOR USE OF POLYVALENT BACTERIOPHAGE IN TECHNIQUE OF DELAYED PRESCRIBING OF ANTIBIOTICS IN PATIENTS WITH ARS

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ABSTRACT

The aim: Of research was to evaluate the effectiveness of bacteriophage in patients with acute rhinosinusitis in respect of technique of delayed prescribing of antibiotics.

Materials and methods: There were examined 155 patients who were given irrigation therapy with isotonic solution of sea water 4 times a day and mometasone furoate of 100 mg twice a day for 10 days. The patients of intervention group (n - 80) were additionally prescribed the polyvalent bacteriophage endonasally, in drops of 2-10 ml 3 times a day.

Results: The patients in the control group were observed the decrease in intensity of rhinorrhea, nasal congestion and post-nasal drip on the third day of supervision ($p < 0.05$), the reduction in bacterial load with Staphylococcus aureus, S. pneumoniae, Haemophilus influenza and M. Catarrhalis ($p <0,005$), the increase of IgA and sIgA levels ($p<0,005$) and the reduction in prescription of antibacterial medications by 20%.

Conclusions: Adding of polyvalent bacteriophage contributes to reducing the use of antibiotics and is recommended in the framework of the strategy of delayed prescribing of antibiotics.

KEY WORDS: acute rhinosinusitis, bacteriophage, delayed prescribing of antibiotics

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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 ABRSmost likely is the stage of evolution of the post-viral one as it is usually followed by ABRS [1,4]. The saprophitic 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 pathogensin respiratory tracts [13-15]. The also express and secretevarious 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. Secretorysystem 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

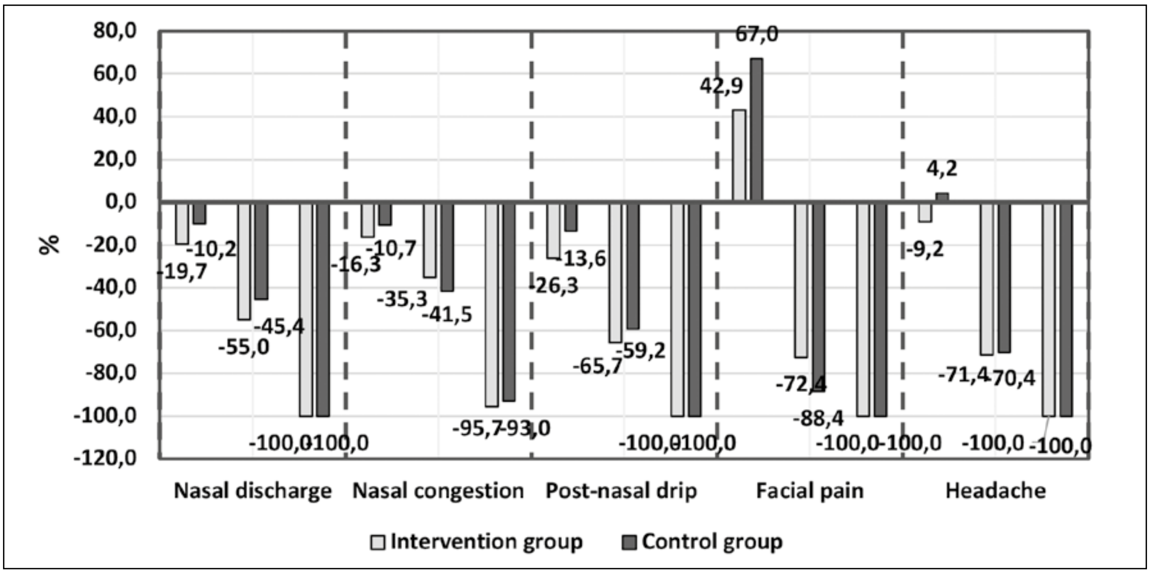

Fig. 1. Relative dynamic regression (%) of APVRS symptoms

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 was36,24 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 3±1) there was evaluation of the state, the decision on antibiotic treatment was made. On the V3 (day 5±1) and on the V4 day (10 ±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 i V4 there was an intake of nasal swabs and blood serum for immunological test (sIgA 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.

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.

Table I. Comparison of the symptom dynamics

Index	dT	Mann Whitney U-test	Wilcoxon W	p-value (double)	Significant difference*
Nasal discharge	dT_2	2171,500	5411,500	0,001	Significant
	dT_3	2128,000	5368,000	0,000	Significant
	dT_4	2800,000	6040,000	0,019	Significant
Nasal congestion	dT_2	949,500	1300,500	0,030	Significant
	dT_3	778,000	3628,000	0,807	Insignificant
	dT_4	850,000	3700,000	0,195	Insignificant
Post-nasal drip	dT_2	2216,000	5456,000	0,002	Significant
	dT_3	2292,500	5532,500	0,001	Significant
	dT_4	2600,000	5840,000	0,001	Significant
Facial pain	dT_2	2667,500	5907,500	0,221	Insignificant
	dT_3	2542,500	5392,500	0,074	Insignificant
	dT_4	2829,000	5679,000	0,489	Insignificant
Headache	dT_2	2656,000	5896,000	0,196	Insignificant
	dT_3	2858,000	6098,000	0,575	Insignificant
	dT_4	2820,500	6060,500	0,427	Insignificant

* Conclusion was made with significance level equal to 0.05

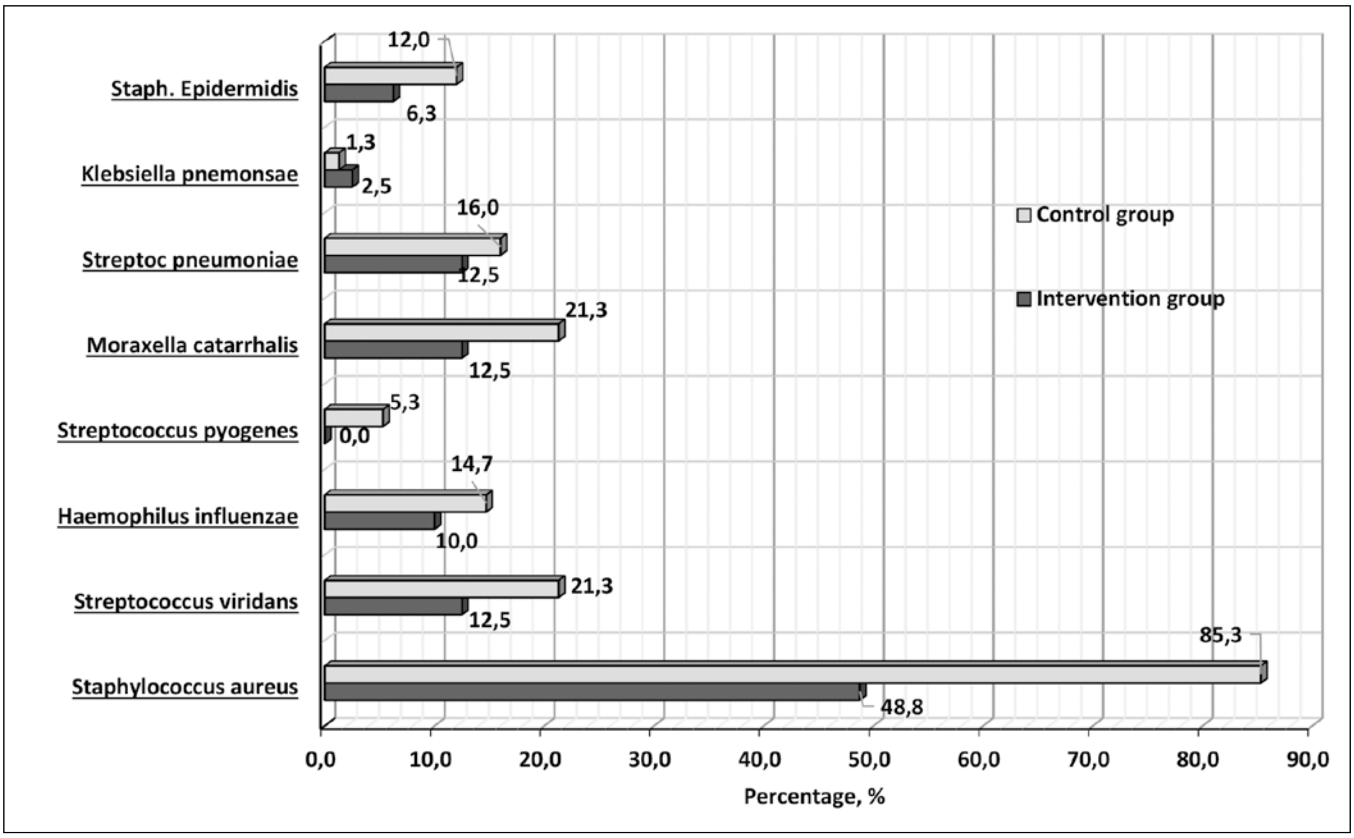

Fig. 2. Analysis of types of microflora in the groups

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.

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

Parameter	Group	N (%)	χ^2	p-value
Number of antibiotic prescriptions	Intervention (n 80)	31 (38,8)	5,377	0,0204
	Control (n 75)	44 (58,7)		

*Conclusion was made with significance level equal to0.05

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

Influential factors	Value	Standard error	Wald test statistics	Number of degrees of freedom	Significance
Intervention group					
Staph. aureus	-0,351	0,809	0,188	1	0,665*
Haem. influenz.	3,569	1,140	9,800	1	0,002
Mor. catarrhalis	3,009	0,884	11,583	1	0,001
Strep. pneumon.	2,371	0,786	9,093	1	0,003
Control group					
Staph.aureus	-0,257	0,517	0,246	1	0,620*
Haem.influenz.	-0,417	0,683	0,372	1	0,542*
Mor.catarrhalis	1,212	0,730	2,757	1	0,097
Strep.pneumon.	-0,696	0,688	1,025	1	0,311*

* statistically significant difference can be seen

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 toχ^2criteria has shown that there is a significant difference in prescription of antibiotics between the patients of the intervention group and the control one (p=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 influenza and Streptococcus pneumonia.

The evaluation of IgA i sIgA levels was fulfilled. The indicators in healthy people were equal to: IgA 1,94±0,87 mg/ml, sIgA 3,74±0,46 mg/l. On the V1 the level of serum IgA was 0,95mg/mlin the intervention group (p<0,05) and 0,89 mg/ml- in the control group. The level of secretory IgA was 1,43mg/lin the intervention group (p<0,05) and 1,19 mg/lin the control group (p<0,05in comparison with healthy people in both groups). In the course of treatment, the increased level of indicators of serum IgA up to 2,29 mg/ml in the intervention group and up to 1,88 mg/ml in the control group can be seen.

The dynamics of increased sIgA level showed 4,03mg/l in the intervention group and 2,82 mg/l in the control group. 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 (p<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% (p<0.005). The reduction in the number of antibiotic prescriptions correlates with normalization of species composition of bacterial flora. Staphylococcus

Table IV. Comparison of dynamics of IgA and sIgA levels between the groups

Parameter	t-statistics	Number of degrees of freedom	p-value (double)	Difference of average	Difference *
IgA (V1)	0,628	153	0,530	0,05	Insignificant
IgA (V4)	5,741	153	<0,001	0,41	Significant
sIgA (V1)	1,619	153	0,107	0,24	Insignificant
sIgA (V4)	5,140	153	<0,001	1,21	Significant

*Conclusion was made with significance level equal to 0,05

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 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 i 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 вprescription of antibiotics.

REFERENCES

1. Fokkens W.J., Lund V.J., Hopkins C. et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology.2020; 58(29): 1-464. doi: 10.4193/Rhin20.600.
2. Bachert C., Hörmann K., Mösges R. et al. An update on the diagnosis and treatment of sinusitis and nasal polyposis. Allergy. 2003;58:176-91.
3. Hoffmans R., Wagemakers A., van Hellings P. Acute rhinosinusitis and allergic rhinitis to comorbidity, ethnicity and environment. PLoS One. 2018;13(2):e0192330.
4. Fokkens W.J., Lund V.J., Mullol J. et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinology. 2012;50:1-12.
5. Rosenfeld R.M., Piccirillo J.F., Chandrasekhar S.S. et al. Clinical practice guideline (update): Adult sinusitis. Otolaryngology - Head and Neck Surgery. 2015;152(2):1-39.
6. Eloy P., Poirrier A.L., De Dorlodot C. et al. Actual concepts in rhinosinusitis: a review of clinical presentations inflammatory pathways, cytokine profiles, remodeling, and management. Curr Allergy Asthma Rep. 2011;11:146-62.
7. Tan K.S., Yan Y., Ong H.H. et al. Impact of Respiratory Virus Infections in Exacerbation of Acute and Chronic Rhinosinusitis. Curr Allergy Asthma Rep. 2017;17:24.
8. Payne S.C., Benninger M.S. Staphylococcus aureus is a major pathogen in acute bacterial rhinosinusitis: a metaanalysis. Clinical Infectious Diseases. 2007 Nov 15;45(10):e121-7.
9. Brook I. Bacteriology of acute and chronic frontal sinusitis. Archives of otolaryngology-head & neck surgery. 2002;128(5):583-5.
10. Braciale T.J., Sun J., Kim T.S. Regulating the adaptive immune response to respiratory virus infection. Nature Reviews Immunology. 2012;12:295-305.
11. Kolesnikova L., Heck S., Matrosovich T. et al. Influenza virus budding from the tips of cellular microvilli in differentiated human airway epithelial cells. The Journal of general virology. 2013;94:971-6.
12. Yan Y., Tan K.S., Li C. et al. Human nasal epithelial cells derived from multiple subjects exhibit differential responses to H3N2 influenza virus infection in vitro. The Journal of allergy and clinical immunology. 2016;138(1):276-81.
13. Yan Y., Gordon W.M., Wang D.Y. Nasal epithelial repair and remodeling in physical injury, infection, and inflammatory diseases. CurrOpinOtolaryngol Head Neck Surg. 2013;21:263-70.
14. Wang D.Y., Li Y., Yan Y. et al. Upper airway stem cells: understanding the nose and role for future cell therapy. Curr Allergy Asthma Rep. 2015;15:490.
15. Watelet J.B., Van Zele T., Gjomarkaj M. et al. Tissue remodelling in upper airways: where is the link with lower airway remodelling? Allergy. 2006;61:1249-58.
16. Clay C.C., Reader J.R., Gerriets J.E. et al. Enhanced viral replication and modulated innate immune responses in infant airway epithelium following H1N1 infection. J Virol. 2014;88:7412-25.
17. Wang Z., Wan Y., Qiu C. et al. Recovery from severe H7N9 disease is associated with diverse response mechanisms dominated by CD8+ T cells. Nature Communications. 2015;6:6833.
18. Mikhailenko H.V., Kolyada T.I., Vdovichenko N.I. Zminy pokaznykiv rivnya sekretornoho imunohlobulinu A u khvorykh na zapal'ni protsesy VDSH riznoyi etiolohiyi [Changes of indicators of the levels of secretory immunoglobulin A in patients with inflammatory processes URT of different etiology]. Bulletin of Problems in Biology and Medicine. 2013;2(99):137-39. (in Ukrainian).
19. Bird J., Biggs T.C., Thomas M. et al. Adult acute rhinosinusitis. BMJ. 2013;346:2687. doi: https://doi.org/10.1136/bmj.f2687.

20. McCullough A.R., Pollack A.J., Hansen M.P. et al. Antibiotics for acute respiratory infections in general practice: comparison of prescribing rates with guideline recommendations. Med J Aust. 2017;207(2):65-69. doi: 10.5694/mja16.01042.
21. Spurling G.K.P., Del Mar C.B., Dooley L. et al. Delayed antibiotic prescriptions for respiratory infections. Cochrane Database of Systematic Reviews. 2017 Sep 7;9(9):CD004417. https://www. cochranelibrary. com/cdsr/doi/10.1002/14651858.CD004417.
22. Nakaz M.O.Z. Ukrayiny vid 11 lyutoho 2016 r. № 85. Unifikovanyy klinichnyy protokol pervynnoyi, vtorynnoyi (spetsializovanoyi) ta tretynnoyi (vuz'kospetsializovanoyi) medychnoyi dopomohy. Hostryy rynosynusyt [Resolution of MHU of Ukraine of 11 February 2016 No. 85. Unified clinical guideline for the primary, secondary (specialized) and tertiary (highly specialized) medical care. Acute rhinosinusitis]. http://mtd.dec.gov.ua/images/dodatki/2016_85_GRS/2016 _85_ YKPMD_GRS.pdf. (in Ukrainian).
23. Krasilnikov I.V., Lysko K.A., Otrashevska E.V. et al. Preparaty bakteriofagov: obzor sovremennogo sostoyaniya i perspektiv razvitiya [Bacteriophage preparations: review of the current status and development prospects]. Siberian Medical Journal. 2011;26(2):33-7. (in Russian).
24. Weber-Dabrowska B., Zimecki M., Kruzel M. et al. Alternative therapies in antibiotic-resistant infection. Advances in Medical Sciences. 2006;51:242-4.

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