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REVIEW

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Delayed prescription of antibiotics and the capabilities of herbal medicine when used in respiratory infections

V. I. Popovych[1*] and I. V. Koshel[2]

Abstract

Background Excessive and improper use of antibiotics in respiratory infections is still an urgent issue. In most cases of ARS and AT, antibiotics can be considered excessive treatment, since they are a completely inappropriate solution for viral infections. An important issue is negative changes to the microbiome in the patient's body, which cause a negative impact on health, and abnormal changes can last longer and be more severe than the disease itself. Misuse of antibiotics can be harmful, especially in children, because the long-term effects of antibiotics on the macroorganism and microbiome can cause the disease to recur in adulthood.

Main part Sinupret® in the strategy of delayed prescription of antibiotics in ARS patients as part of a controlled study helps reduce prescription of antibacterials by 1.81 times and by 15.5 times (53% to 3.4%) versus statistics. Imupret® in patients with severe acute tonsillitis when employing the approach of delayed antibiotics prescription reduces the need for antibacterial therapy by 43.7% or 2.3 times, and by 11 times (72% to 10.1%) versus the average statistical level of prescription. Unlike antibiotics, herbal medicines positively affect the patient's microbiome and have a favourable safety profile.

It is imperative to increase knowledge and awareness, as well as provide appropriate training and communication strategies among physicians to prevent overuse and misuse of antibiotics.

Conclusion Herbal medicinal products BNO1016 (Sinupret®) and BNO1030 (Imupret®) can be considered as an alternative to antibiotics for the treatment of uncomplicated forms of acute rhinosinusitis and acute tonsillitis. Evidence shows that herbal medicines are effective and have a favourable safety profile. However, herbal medicinal products cannot replace antibiotics in all the cases, so delayed prescription of antibiotics with pre-treatment using herbal products can help reduce excessive and unjustified use of antibiotics.

Keywords Respiratory infections, Treatment, Herbal medicinal products, Delayed prescription of antibiotics

Introduction

Acute rhinosinusitis (ARS) and acute tonsillitis (AT) are acute respiratory infections and the most frequent diseases in humans, especially in childhood, and besides discomfort and a deterioration in the patient's quality of life, have great social and economic significance. It is this group of diseases that is one of the leading causes of a significant number of days missed at school and clinic visits [1–3]. ARS, AT are inflammatory diseases, and in most cases are viral. A viral infection usually triggers the inflammatory cascade in the context of the common cold.

Acute viral RS (AVRS), or the common cold, has a very high incidence — from 2 to 5 episodes per person per year [4]. This incidence in children is four times

*Correspondence:
V. I. Popovych
popovych_ent@ukr.net
[1] Lviv Medical University, Lviv, Ukraine
[2] Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine

higher and is one of the main reasons for primary care visits [5, 6]. Acute post-viral RS (APVRS) is less common. A recent study established an incidence of 18.8 episodes per 1000 persons of the general population per year [7]. AT occurs in all age groups, but more often between 5 and 15 years and accounts for about 5% of all clinic visits [2, 8].

The most difficult issue is the correct diagnosis of bacterial ARS or AT. Acute bacterial RS (ABRS) develops in rare cases: in only 0.5–2% of all AVRS cases, this inflammatory condition can develop into a bacterial infection [1]. Acute bacterial tonsillitis (ABT) occurs in immunocompetent children in 20–30% of cases, in adults — in 5–15%, and its main cause is β-hemolytic group A streptococcus (GAS) [8].

Today, there is no standard criterion for the differential diagnosis between bacterial ARS and AT and their non-bacterial forms. Based on the comprehensive differentiation of viral and bacterial aetiology, criteria assessing the presence or absence of a number of history data and clinical symptoms are proposed. EPOS 2020 recommends using a combination of symptoms to determine the likelihood of a bacterial process and confirms ABRS when 3 or more of the following five criteria are met: deterioration of symptoms after the initial improvement, fever over 38 °C, pronounced local soreness and nasal discharge (mainly purulent), as well as increased CRP/ESR. Guidelines for tonsillitis for stratification of patients with no need to prescribe antibacterial therapy recommend using McIsaac score (maximum 5 points). All clinical guidelines are unanimous that normally there is no need for additional diagnostic tools to differentiate viral from bacterial processes, and the previously recommended blood test to measure CRP/ESR did not result in a decreased prescription of antibiotics [1, 8]. However, reliable laboratory tests for bacterial infections are still under study [9]. Real-life differential diagnosis between bacterial ARS or AT and their non-bacterial forms often leads to overdiagnosis, which in turn causes overuse of diagnostic tests and early unnecessary prescription of antibiotics [10, 11].

Antibiotic overuse and related problems

According to the literature, unjustified antibacterial therapy is prescribed in 54% to 77% of ARS and AT cases [12]. In Ukraine, paediatricians prescribe antibiotics in 53% of cases, general practitioners in 32%, otolaryngologists in 77% of cases; for AT, paediatricians prescribe antibiotics in 53% of cases, general practitioners in 72%, and otolaryngologists in 64% [13].

The unjustified prescription of antibiotics is one of the main causes of the global issue of antimicrobial resistance, as, according to WHO, inadequate therapy with antibiotics is prescribed in an average of 50% of cases globally [14, 15]. In addition to the issue of antimicrobial resistance, which in 2019 caused an estimated 1.27 million deaths worldwide, the unjustified prescription of antibiotics can be harmful to a particular patient [16]. The unjustified prescription of antibiotics for viral tonsillitis, in particular, associated with the Epstein-Barr virus, is characterised by a high incidence of severe generalized rashes involving the extremities — amoxicillin-associated rash [17]. Antibacterial therapy, even when administered as indicated, causes long-term changes in the bacterial microbiome of the body, so it can disrupt the symbiosis between the microbiome and the macroorganism. Studies have shown significant changes in the gastrointestinal microbiome not only after 7 days, but also after 11 weeks after the discontinuation of antibiotics, indicating long-term damage to the microbiome. After 11 weeks, although the microbial composition changes compared to day 7, it does not return to its initial level, and potentially useful species of microorganisms, such as *Akkermansia muciniphila*, do not re-appear, even with long-term observation [18]. Recent studies show that the microbial communities living on the epithelial surfaces of the nasal passages are a key factor in maintaining a healthy microenvironment, influencing both pathogen resistance and immune responses [19]. A microbiological study of healthy individuals shows that the basis of the normal respiratory microbiome of the nasopharynx consists of commensal microorganisms: anaerobes: Lactobacillus spp., Bifidobacterium spp., and aerobes: *S. salivarius* and *S. viridans*, which are tested at a high population level (Table 1).

Patients with chronic recurrent nasopharyngitis with history of several courses of antibacterial therapy, show significant changes in the respiratory microbiome: a decrease in the population level of commensal microorganisms, with background colonization by opportunistic microorganisms (Staph. aureus, Staph. epidermidis, *E. coli*, Strept. Pyogenes) and pathogenic species of bacteria (Pneumococcus pneumoniae, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) in association with Candida fungi [20]. Changes in oral, respiratory, skin, urogenital, vaginal, or gastrointestinal microbiome can have potentially dangerous effects, including sensitization, periodontal disease and cavities in children, opportunistic infections, vaginal candidiasis, carcinogenesis activation, etc. To this date, a whole group of diseases caused by antibiotics has been identified [21]. Excessive and improper use of antibiotics and its subsequent effect on the microbiome in young children can cause the disease to manifest at a later age [22, 23]. A disrupted microbiome can contribute to chronic, low-grade

Table 1 Characteristics of the nasopharyngeal microbiome in healthy individuals and CNP patients

Population level of microorganisms (CFU/mL)				
Microorganisms		Control	Before treatment	After treatment
Commensal flora	Lactobacillus spp.	7.75 ± 0.20[a]	4.88 ± 0.06[a]	6.94 ± 0.17
	Bifidobacterium spp.	5.72 ± 0.18[a]	4.11 ± 0.13[a]	5.24 ± 0.17
	S. salivarius	6.78 ± 0.32[a]	4.54 ± 0.2[a]	6.87 ± 0.19
	S. viridans	2.58 ± 0.06[a]	3.47 ± 0.06[a]	2.47 ± 0.07
Opportunistic flora	Staph. aureus	–	4.51 ± 0.12[a]	2.76 ± 0.10[b]
	Staph.epidermidis	–	5.27 ± 0.16[a]	2.70 ± 0.08[b]
	Strept. pyogenes	–	5.66 ± 0.14	3.01 ± 0.06[b]
	Escherichia coli	–	3.45 ± 0.12[a]	–
Pathogenic flora	Pneum. pneumoniae	–	3.86 ± 0.07[a]	–
	Haem. influenzae	–	3.99 ± 0.01[a]	–
	Pseudom. aeruginosa	–	4.56 ± 0.25[a]	–
	Klebs. pneumoniae	–	4.86 ± 0.13[a]	–
Fungal flora	Candida	–	2.89 ± 0.19[a]	–

[a] *There is a statistically significant difference from the control*

[b] *There is a statistically significant difference between groups*

systemic inflammation, thus even contributing to age-related diseases [24].

The disrupted microbial spectrum of the oral and respiratory microbiome disturbs colonization resistance and supports a slow persistent inflammatory process involving biofilm formation [25]. Biofilms can enhance antimicrobial resistance and bacterial anti-immune properties tenfold, which creates conditions for the progression and persistence of inflammation, and contributes to its frequent recurrence. Studies have found that disruption of the normal nasopharyngeal microbiome composition involving biofilm formation is associated with susceptibility to acute respiratory illnesses and chronic URT diseases [26–28].

Given the urgency of the issue, a number of studies were conducted to establish the justification for antibiotics being overprescribed by physicians. It was found that physicians who treat acute respiratory infections in outpatient settings are well aware of the use of antibiotics and antimicrobial resistance, therefore, they support the responsible use of antibiotics. However, the percentage of inappropriate prescriptions is very high [29, 30]. Additional studies were conducted to examine the factors behind inappropriate antibiotic prescribing practices and a failure to comply with the guidelines. It was determined that the main reasons for that were pressure on the physician due to insufficient knowledge about antibiotics in patients or their parents, patient expectations regarding antibiotics, clinical uncertainty regarding the differentiation between bacterial and non-bacterial processes, low confidence of the physician, fear of complications, lack of informative tests, contacting the physician with s self-bought antibiotic due to its over-the-counter availability, pressure from the workload, as well as inadequate medical training [31–34].

In order to cut down on the misuse of antibiotics for respiratory infections, published studies highlight the importance of strategies that have shown to reduce such improper prescription. These include well-targeted comprehensive educational activities, educational media campaigns targeted at healthcare professionals and the general public, using good communication skills during visits and possibly longer, less pressured consultations, medical testing, and delayed antibiotic prescription tactics, especially if accompanied by written information. Delayed prescription tactic also promotes focused, personalised patient education [35–37].

Tactics of delayed prescription of antibiotics and the capabilities of herbal medicine

The key point of delayed prescription tactics is the healthcare professional assuming that antibiotics do not need to be prescribed immediately, expecting that the symptoms will resolve without them, but leaving the possibility of prescription if the patient's condition does not meet the criteria of positive changes. Patients and physicians may be more willing to accept such a course of treatment compared to the immediate prescription or no antibiotics at all in patients with respiratory infections [38].

Delayed prescription of antibiotics shows an almost similar level of patient satisfaction with treatment when compared to prescribing them at the first visit (86% vs. 91%). This approach helped reduce the frequency

of antibacterial therapy to 31% and does not cause an increase in the number of complications [39, 40].

The main condition for the possibility of implementing the delayed antibiotic prescription strategy is using treatments with proven efficacy. According to the guidelines, symptomatic drug therapy of ARS and AT includes steroidal and non-steroidal anti-inflammatory drugs or antipyretics. However, said symptomatic treatments do not cover the entire spectrum of pathogenetic mechanisms of either ARS or AT, and the prescription of such common treatments as antihistamines, herbal medicinal products, food supplements etc. in acute respiratory infections is not justified, as their benefits have not been proven [41, 42]. Expectations of the antibiotic prescription are highest in patients with poor efficacy of their treatment, especially in the first days. Therefore, there is a need to use products with a complex effect on the main links of pathogenesis and proven efficacy. Medicinal products based on herbs or their extracts generally show a favourable benefit/risk profile and may be a viable alternative for the treatment of uncomplicated respiratory infections [43]. A number of herbal medicinal products have been evaluated for the treatment of acute rhinosinusitis in randomized clinical trials. The efficacy of Sinupret is confirmed by the strongest evidence base, including multicentre clinical studies with sufficient power. Interestingly, evidence for Sinupret appears to be as strong as for synthetic treatments such as mometasone furoate. Sinupret® (BNO 1016) is the only herbal product with evidence generated from well-designed, randomized, controlled trials with adequate power. When speaking about antibiotic misuse, some herbal medicinal products are promising alternatives to conventional treatments and should be considered for acute uncomplicated rhinosinusitis [44]. Therefore, during 8 years between EPOS2012 and EPOS2020, the list of drugs with proven efficacy for ARS expanded to include herbal medicines [1].

In terms of the targeted effect on mitigating the clinical manifestations of AT, the use of herbal medicines could also be promising, since research showed that 28% of physicians prescribe herbal medicines for inflammatory diseases of the pharynx [45]. Echinacea and Pelargonium sidoides products are the most studied in this regard. Randomized trials, however, have not proven their efficacy in patients with acute tonsillitis [46, 47]. The use of phytoneered drug BNO 1030 (Imupret®) for the treatment of acute tonsillitis is promising.

Unlike antibiotics or NSAIDs, treatment with modern combination phytoneered drugs, such as Sinupret and Imupret, usually does not target specific pathogens, although they do have some antiviral and moderate antibacterial effects. Their efficacy is rather based on a multi-target approach to influence the main pathogenetic mechanisms of the disease [48–52]. Many common and recurrent infections, such as upper respiratory tract infections, can be treated using effective and safe herbal medicine options [53, 54].

In EPOS 2020, evidence-based treatment regimens using specific herbal medicines are considered separately for viral and post-viral RS [1]. For example, for AVRS, the working group recommends such herbal medicinal products as BNO1016 (Sinupret®), Cineole (a eucalyptus oil component) and *Andrographis paniculata* SHA-10, as they have a substantial effect on symptoms without significant side effects. For APVRS, BNO1016, Pelargonium sidoides and Myrtol are recommended. These also exert a strong effect on symptoms without causing significant side effects. A significant shortcoming of most herbal medicines is the lack of a uniform effect on the pathogenesis of several forms of ARS, in particular AVRS and APVRS, therefore, they are indicated only for specific nosological entities: viral or post-viral RS. This greatly complicates the prescription of "appropriate medical therapy", since it is not always easy for a physician, especially a primary care physician, to carry out differential diagnosis. Thus, according to guidelines, only BNO1016 is indicated for both acute viral and post-viral RS.

Studies have shown that when Sinupret is prescribed to AVRS patients from Day 1, its transformation into post-viral RS is reduced by 79.5%, and into bacterial RS by 58.7% (Fig. 1). In a similar manner, Sinupret® prescribed to APVRS patients from Day 1 of treatment reduces its transformation into a bacterial form by 29.3% [55, 56].

A paediatric randomized clinical trial showed that the additional use of the phytoneered drug BNO 1030 (Imupret®) for acute tonsillitis significantly improves the clinical symptoms of tonsillitis, provides reliable difference in their severity starting from Day 3 of treatment (Fig. 2) [57]. From Day 6, patients in the Imupret group did not need to use non-steroidal anti-inflammatory drugs (NSAIDs) to treat fever and sore throat. On Day 6 of treatment, patients in the Imupret group showed such an improvement in symptoms that patients of the control group showed only on Day 10 (Fig. 2). Thus, with Imupret®, when used for acute non-bacterial tonsillitis, a therapeutic benefit can be achieved in 4 days.

As known, one of the strategies to cut down on unjustified antibiotic prescriptions is delayed prescription of the drugs, and the main condition for implementing such a strategy is using treatments with proven efficacy. In the context of the strategy of delayed antibiotic prescription, the initial treatment should be highly effective, especially in the first days after its prescription. If the initial treatment has poor efficacy, upon repeated examination, usually on Day 3 of treatment, a need to prescribe

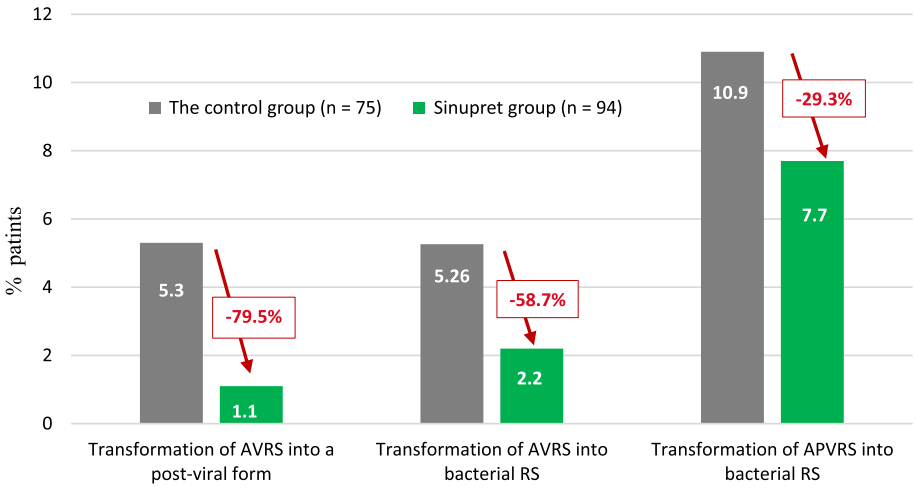

Fig. 1 The efficacy of Sinupret for ARS

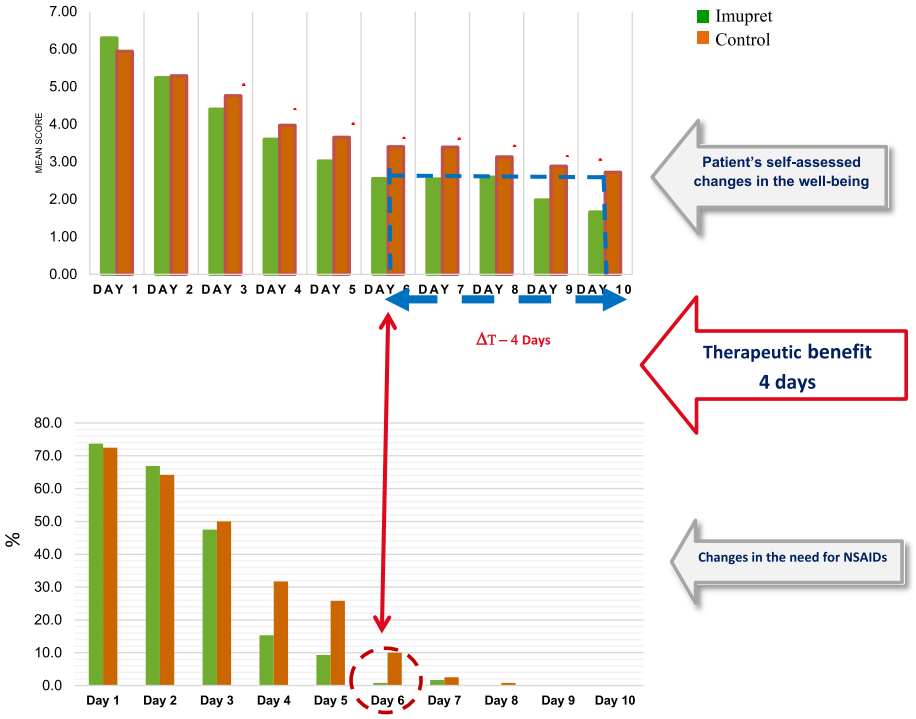

Fig. 2 The efficacy of Imupret for AT

antibacterials arises. Completed studies showed that phytoneered drugs Sinupret® and Imutret® exert a proven therapeutic effect in the first days of treatment already. Therefore, the purpose of further research was to evaluate the efficacy of the additional use of phytoneered herbal extracts Sinupret® and Imupret® as part of the approach of delayed antibiotic prescription in patients with acute rhinosinusitis and tonsillitis, compared to standard symptomatic therapy according to clinical guidelines.

The controlled study showed that delayed prescription of antibiotics in patients on standard ARS treatment was employed in 8.26% of cases, and in patients on Sinupret — in 3.4% of cases (Fig. 3) [58].

This incidence of antibiotic prescriptions generally corresponds to existing guidelines regarding the need to

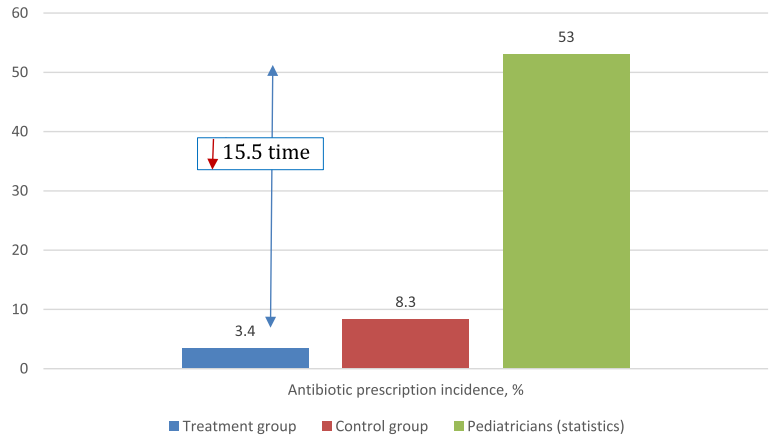

Fig. 3 Efficacy of Sinupret® in delayed antibiotic prescribing strategy

prescribe antibacterial therapy for this disease ([1, 10], etc.). At the same time, the literature review showed that, in Ukraine, paediatricians prescribe antibiotics in 53% of cases, general practitioners in 32% of cases, and otolaryngologists in 77% of cases [13]. Thus, Sinupret® in the strategy of delayed prescription of antibiotics in ARS patients helps reduce justified prescription of antibacterials by 1.81 times and by 15.5 times (53% to 3.4%) versus statistics.

A randomized study of the efficacy of Imupret® versus standard therapy according to clinical guidelines as part of the strategy of delayed antibiotic prescription was conducted in patients with severe acute tonsillitis (McIsaac score of 4–5) [8]. The study showed that, according to the approach of delayed prescription, antibiotics were prescribed to 23.46% of patients on standard therapy according to clinical guidelines (14.28% on Day 3 of treatment and 9.18% on Day 5) (Fig. 4) [57].

The number of prescriptions in a controlled study matched the average incidence of bacterial tonsillitis [8, 11]. In patients on additional Imupret®, antibacterial therapy was prescribed to 10.12% of patients (6.06% on Day 3 of treatment and 4.04% on Day 5) (Fig. 4). Thus, the important conclusion of this study is that in the controlled settings, Imupret® in patients with severe acute tonsillitis reduces the need to prescribe antibacterial therapy when employing the approach of delayed antibiotic prescription by 43.7% or 2.3 times versus patients on standard treatment. At the same time, in Ukraine, paediatricians prescribe antibiotics in 53% of AT cases, general practitioners in 72% of cases, and otolaryngologists in 64% of cases [13]. The obtained results show an 11-fold decrease in the antibiotic prescriptions when compared

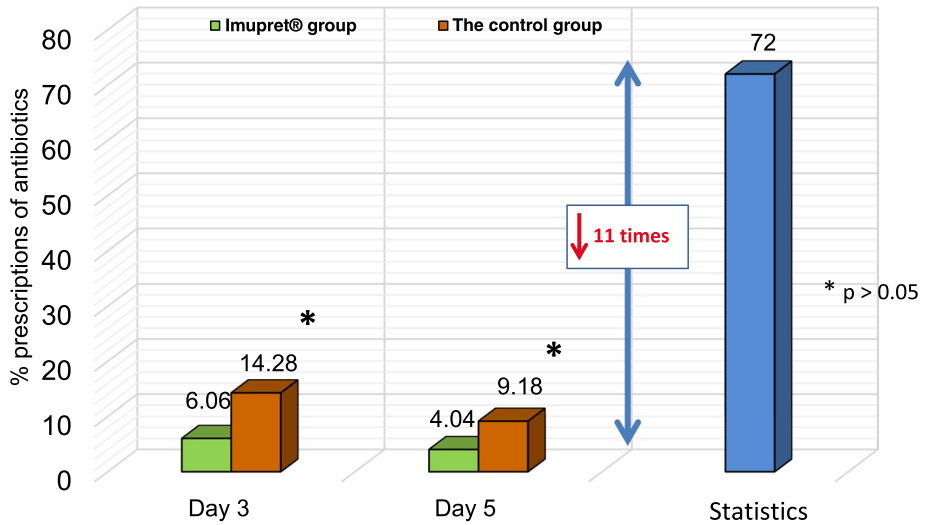

Fig. 4 Efficacy of Imupret in delayed antibiotic prescription in AT patients

to the average statistical level of their prescription by general practitioners.

Thus, Imupret® in the strategy of delayed prescription of antibiotics in AT patients helps reduce justified prescription of antibacterials by 2.3 times and by 11 times versus statistics.

As known, antibacterial therapy causes long-term changes in various types of the bacterial microbiome. Given that, a study of the effect of phytoneered drugs Sinupret® and Imupret® on changes in the microbiome was carried out, since the preservation of the microbiome corresponds to the strategy of reasonable antibiotic use. An experimental study showed that the bacterial gut microbiome of laboratory mice treated with BNO 1011 (Sinupret®) was highly similar to the one of untreated mice, which indicates no effect on the microbiome [18].

A clinical study devoted to evaluating the efficacy of Imupret® in patients with chronic nasopharyngitis and history of repeated prescription of antibacterials showed that the phytoneered drug promotes the improvement of the nasopharyngeal microbiome composition. There was a reliable microbiological increase in the level of commensal flora, almost to normal levels: Lactobacillus spp., Bifidobacterium spp., *S. salivarius*, *S. viridans* (Table 1). After treatment, a statistically significant reduction in Strept. Pyogenes and other representatives of opportunistic microflora was observed: Staph. Aureus, *S. epidermidis*. There was no colonization of *E. coli* and other pathogenic bacteria: Pneumococcus pneumoniae, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, as well as Candida fungi [59]. The improved characteristics of the respiratory microbiome are associated with improvement in clinical symptoms.

Therefore, studies with phytoneered drugs Sinupret® and Imupret® showed that treatment with herbal medicinal products is effective in improving ARS and AT symptoms, and, therefore, it gives the opportunity to cut down on prescribing antibiotics to patients, while having a favourable safety profile. These studies contributed to the recognition of herbal medicinal products in official guidelines for rhinosinusitis [1].

Conclusion

Excessive and improper use of antibiotics is still an urgent issue. Another important issue is antimicrobial resistance, which in 2019 caused an estimated 1.27 million deaths worldwide. Antibiotics can cause harmful changes in the microbiome and the macroorganism, with a subsequent negative impact on health that may last longer and be more severe than the disease itself. In most cases of ARS and AT, antibiotics can be considered excessive treatment, since they are a completely inappropriate solution for viral infections. Misuse of antibiotics can be harmful, especially in children, because the effects of antibiotics on the macroorganism and microbiome can cause the disease to recur in adulthood. Moreover, frequent clinic visits, which are also associated with higher incidence of antibiotic prescription, can draw off resources from treating potentially more serious illnesses.

Herbal extracts with proven efficacy today can be considered as an alternative to antibiotics for the treatment of uncomplicated respiratory infections. Evidence shows that herbal medicines are effective and have a favourable safety profile. However, herbal medicinal products cannot replace antibiotics in all cases, so delayed prescription of antibiotics with pre-treatment using herbal products can help reduce excessive and unjustified use of antibiotics.

Therefore, there is consensus in the literature regarding strategies that have been shown to reduce antibiotic consumption in acute respiratory infections. Large-scale implementation of these strategies in medical practice is mandatory. It is imperative to increase knowledge and awareness, as well as provide appropriate training and communication strategies among physicians to prevent overuse and misuse of antibiotics. While awareness of the effective use of antibiotics is growing, developing a broader understanding of responsible antibiotic use and the use of herbal medicines in routine practice still plays an important role in reducing the risk of side effects and antimicrobial resistance, as well as promoting more conscious choice of treatments for inflammatory UTIs.

To sum it up, the purpose of this review is to highlight the part herbal medicines play in the effective treatment of ARS and AT and the reduction of unjustified antibiotic prescription.

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Authors' contributions
VP, IK - participated in the protocol and documentation development of the studyes, solving of organizational issues, coordination with other investigators and manuscript writing. All the authors participated in recruiting, treating patients and registering study data.

Authors' information
VP: doctor of medical sciences, professor, the head of the Department of Surgery No. 1 of Lviv Medical University, expert of the Ministry of Health of Ukraine in the field of Otolaryngology. Children's otolaryngology. Surdology.
IK: Department of ENT Diseases, Head and Neck Surgery, Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
The studyes were approved by the Ethics Committee of Ivano-Frankivsk National Medical University.

Consent for publication
All authors read and approved the final manuscript and gave consent to publication.

Competing interests
The authors declare that they have no competing interests in this section.

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