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Multicenter, randomized, open-label, comparative study of the effectiveness of nasal spray Aqua Maris Extra Strong as a symptomatic therapy in the technology of delayed antibiotic prescription in the treatment of acute rhinosinusitis in children aged 6–11 years.

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ABSTRACT

Antibacterial therapy in acute rhinosinusitis (ARS) is prescribed 4–9 times more often than recommended, while no >5 % of patients require such treatment. The main motive for the irrational antibiotic prescription is the presence of mucopurulent discharge and nasal congestion in combination with hyperthermia.

The study objective was to determine the efficacy of hypertonic seawater solution in the technology of delayed antibiotic prescription in patients with ARS.

Methods: In a multicenter, randomized, open-label, comparative study, 100 children were randomized. 100 children with ARS aged 6–11 years, who received Aqua Maris Extra Strong irrigation therapy in addition to standard therapy or received standard therapy, completed the study.

Evaluation criteria: decreased intensity of nasal congestion, rhinorrhea, postnasal drip, headache and facial pain, assessed by the physician using a 4-point scale at each visit compared to Visit 1, dynamics of self-scored symptoms using a 10-point visual analogue scale, frequency of antipyretic and antibiotic prescription.

Results: The use of hypertonic seawater solution in patients with ARS provides a clinically significant reduction in the severity of core or key symptoms: rhinorrhea, nasal congestion, postnasal drip and headache, assessed by the physician at V2 ($p < 0.05$). There are significant differences in the dynamics of these symptoms according to the patient's self-assessment from treatment Day 2 ($p < 0.05$).

The use of irrigation therapy with Aqua Maris Extra Strong in the technology of delayed antibiotic prescription in patients with ARS allows to reduce the prescription of antibacterial drugs. No on-treatment side effects were observed in any patient.

Conclusion: Hypertonic seawater solution Aqua Maris Extra Strong is a safe and effective medicinal product for the symptomatic treatment of acute rhinosinusitis in children aged 6–11 years. It provides a significant therapeutic effect when prescribed in addition to standard therapy and helps to reduce the need for antibiotics.

1. Introduction

Acute rhinosinusitis (ARS) is the most common respiratory infection. The concept of "rhinosinusitis" has been widely used since 2005, since it has been proven that the inflammatory process develops in the nasal cavity and paranasal sinuses simultaneously [1]. In subsequent years, a lot of studies on ARS have been conducted and summarized in the European Position Paper on Rhinosinusitis and Nasal Polyps, EPOS 2020 [2]. According to modern views, the concept of ARS includes three nosological forms: acute viral, post-viral and bacterial rhinosinusitis.

Current guidelines define ARS as the sudden onset of two or more typical clinical symptoms, lasting <12 weeks, one of which must be "core" or "key": nasal congestion/obstruction or nasal discharge (rhinorrhea or postnasal drip), as well as concomitant symptoms: ± facial

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pain/pressure and ± reduction or loss of smell, and cough (day and night) in children. Other symptoms include fever, fatigue and headache [2]. Acute viral rhinosinusitis is defined as the presence of symptoms within up to 10 days without their worsening after the 5th day. Acute post-viral rhinosinusitis is diagnosed when symptoms worsen after the 5th day or persist after the 10th day [2]. In the United States, if symptoms worsen after the 5th day or persist after the 10th day, acute non-viral rhinosinusitis is diagnosed [3]. Thus, the terms "acute post-viral RS" and "acute non-viral RS" in European (EPOS) and US guidelines were chosen to indicate that most cases of ARS are not bacterial. Only about 0.5–5 % of ARS cases may be characterised as acute bacterial rhinosinusitis (ABRS) [2,3].

To date, there is no single standard parameter for the differential diagnosis between non-bacterial (viral, post-viral) and bacterial ARS. Conventional radiography is not informative, CT is not indicated unless the disease persists despite treatment or complications are suspected, and the use of reactive protein tests recommended in EPOS 2012 has not reduced irrational antibiotic prescription [2,4,5]. In this regard, ARS is one of the most common diagnoses for antibiotics to be prescribed. They are prescribed 4–9 times more often than the guidelines recommend, which is one of the main causes of the global problem of antibiotic resistance [6,8,9]. The driving force behind the irrational antibiotic prescription by physicians and the desire among patients to get antibiotic therapy is an abundance of caution in the presence of core ARS symptoms in the first place, such as nasal congestion and mucopurulent discharge from the nasal cavity [7].

An important strategy to reduce the number of irrational prescriptions is to delay prescribing antibiotics. Patients and physicians may be more likely to accept this treatment course than immediate treatment or the lack of antibiotic treatment in people with respiratory tract infections [10].

As part of this strategy and in order to avoid the irrational antibiotic use, you should separately consider the desire to get rid of mucopurulent discharge and nasal congestion, objective indications for antibiotic therapy and the treatment prescription with proven efficacy without antibiotics. However, such widely used medicinal products as decongestants, antihistamines, homeopathic drugs and mucolytics in ARS have not proven effective [1,2].

Based on this, there is a need to use drugs for systemic and local therapy with complex action, which have an effective evidence base for non-bacterial forms of ARS. According to EPOS 2020, pharmacotherapy for non-bacterial forms of ARS (viral / post-viral) with 1^{b}evidence level includes the phytoextract of five herbs "BNO 1016" and therapeutic irrigation with isotonic seawater solution [2,11,12]. Based on the recommendations of most European and American professional associations, seawater (alone or in combination with other medicinal products) plays an important role in the treatment of numerous diseases of the upper respiratory tract (URT), primarily acute and chronic rhinosinusitis, allergic rhinitis in various groups of patients, from pregnant women and children to adults [2,13–15].

The mechanism of action of isotonic seawater solutions is based on two principles: physical and physiological. The first principle is based on the physical (mechanical) effect of cleansing the nasal mucosa from accumulated secretions and pathogens. The second principle depends on the influence of ions on the mucous membrane of the respiratory tract. Trace elements Ca and Mg activate the function of the ciliated epithelium; Na, Cl and Br provide an antiseptic effect; Zn and Se stimulate the production of lysozyme, interferons and immunoglobulins; iodine activates the production of protective mucus by goblet cells [16–19].

Clinical evidence suggests that the inclusion of isotonic seawater in the treatment regimen for ARS in children improves nasal breathing, reduces mucosal oedema and reduces the amount of discharge from the nasal cavity [20,21]. The combination of clinical effects of seawater in combination with a hypertonic solution allows for an additional osmolar effect in allergic rhinitis — a more significant decrease in mucosal oedema [22,23].

In light of these data, the use of hypertonic solutions in ARS might be of interest. There are few data in the literature on the hypertonic solution efficacy for the treatment of chronic rhinosinusitis [24,25]. At the same time, no multicenter studies on the use of hypertonic seawater solutions in the treatment of acute RS in school-age children (6–11 years old) have been previously conducted in terms of compliance with GCP standards. Confirmation of the high efficacy of this medicinal product in the treatment of ARS in children, comparable with other respiratory diseases, would serve as a rationale for optimizing the treatment regimen for this nosology and reducing the number of irrational antibiotic prescriptions.

The aim of this study was to evaluate the efficacy of Aqua Maris Extra Strong hypertonic seawater solution for use in a strategy of delayed antibiotic prescription in school-age children (6–11 years) compared with patients receiving standard symptomatic therapy for ARS according to international and national recommendations [2,26].

2. Materials and methods

2.1. Trial design

Open-label, exploratory, comparative, multicenter, randomized, prospective, parallel-group study was conducted in three outpatient facilities in Ukraine from September 2021 to February 2022. The study was conducted in accordance with the GCP standards and the Declaration of Helsinki.

2.1.1. Registration

Ethics Committee of Ivano-Frankivsk National Medical University, Protocol No. 122/21 as of 09 June 2021.

The study was approved by the Ethics Committee at all study sites. The parents of each child gave their written consent to participate in the study.

2.2. Participants

106 outpatient subjects were enrolled. 100 outpatient subjects aged 6–11 years diagnosed with ARS were randomized. Diagnostic and differential diagnostic criteria were evaluated. The treatment was prescribed in accordance with the recommendations presented in European and national clinical guidelines [2,26]. The clinical diagnosis of ARS was based on the presence of one or more core symptoms: nasal congestion/obstruction or nasal discharge (anterior rhinorrhea or post-nasal drip) plus ± facial pain/pressure and ± cough (day and night) within <12 weeks.

Inclusion criteria:

- Male and female outpatient subjects aged 6–11 years diagnosed with ARS;
- persistence of symptoms within 10 days from the disease onset or worsening of the condition after the 5th day of treatment, in the absence of diagnostic criteria for acute bacterial RS;
- severity of symptoms with a total value of 6 to 10 scores according to the MSS scale (Main Symptoms Severity score): nasal discharge and its nature, nasal congestion, drip of discharge along the back of the throat, facial pain, headache (0 — no symptom, 1 — minor manifestation, 2 — moderate manifestation, 3 — severe manifestation, 4 — very severe manifestation);
- willingness and ability of the patient and (or) parents to comply with the requirements of the Study Protocol;
- signed informed consent;
- lack of exclusion criteria.

Exclusion criteria:

- intake of one of the forms of investigational medicinal products within 30 days before the ARS onset;
- diagnosis of allergic rhinosinusitis;
- known drug intolerance;
- >14 days from the disease onset;
- severe course requiring hospitalization or antibiotic therapy (>10 scores according to MSS scale);
- the presence of immunodeficiency states, chronic pathology and anatomical anomalies of the osteomeatal complex, which can affect the disease outcome.

Withdrawal criteria:

- the decision of the patient and/or parents to discontinue participation in the study and withdrawal of written informed consent;
- loss of contact with the patient;
- individual intolerance to the study medicinal product and the reference treatment regimen;
- the occurrence of serious and/or unforeseen adverse events/reactions in a patient during the study;
- the development of complications of the underlying disease, which in the physician's opinion require patient's withdrawal from the study;
- patient's violation of the procedures provided by the Protocol.

50 patients were randomized in the treatment group: patients who received endonasal irrigation therapy with Aqua Maris Extra Strong (AMES) since the diagnosis of acute RS was established plus symptomatic therapy with a complex phytopreparation BNO 1012 (per os).

50 patients were randomized in the control group: patients who received endonasal irrigation therapy with isotonic saline solution since the diagnosis of acute RS was established plus symptomatic therapy with a complex phytopreparation BNO 1012 (per os).

The following patients ($n = 50$) were randomized in the treatment group: 25 (50.0 %) boys and 25 (50.0 %) girls (mean age — 8.16 ± 1.72). The following patients (n = 50) were randomized in the control group: 30 (60.0 %) boys and 20 (40.0 %) girls (mean age — 8.12 ± 1.84).

The patients of two groups were of similar sex, age, clinical manifestations of the disease ($p > 0.05$).

2.3. Interventions

Since the moment of randomization all patients received therapy with a complex phytopreparation BNO 1012 (per os) and (if indicated) symptomatic medications (paracetamol).

Patients in the control group additionally received therapeutic irrigation of the nasal cavity with isotonic saline solution, 1–2 instillations in each nasal passage 3–4 times a day.

Patients in the treatment group additionally received therapeutic irrigation of the nasal cavity with AMES, from one batch, 1–2 instillations in each nasal passage 3–4 times a day. AMES is a nasal spray of a hypertonic sterile solution of Adriatic seawater with natural salts and trace elements in a container with a dosing device.

Name and address of the manufacturer: JADRAN – GALENSKI LABORATORIJ D.D. Svilno 20 51,000 Rijeka Croatia.

The drug is registered in Ukraine and available over-the-counter (OTC). Therefore, formulation, manufacturing process, packaging and labelling of the drug comply with GMP and current national requirements of Ukraine. A detailed description of all aspects of the quality and safety of AMES is part of the corresponding product characteristics. In Ukraine, approved indications for use are: the need to thin and improve the outflow of thick mucus in case of swelling and nasal congestion, to reduce the local inflammatory process and to reduce the risk of complications in acute and chronic diseases of the nasal cavity (rhinitis, sinusitis).

ENT practitioners with experience of at least 5 years were involved in the study.

2.4. Outcome measures

All data were evaluated at the beginning of the study and within 10 days (Table 1).

Symptoms were assessed by physicians and patients. At each visit, physicians evaluated three principal symptoms according to the MSS scale: (0 to 4 points for each symptom): rhinorrhea, nasal congestion, postnasal drip, facial pain and headache. In addition, patients and their parents daily assessed complaints in a diary (rhinorrhea, nasal congestion, post-nasal drip, facial pain and headache) in points using a 10-point visual analogue scale.

At Visits 2–3 (V_2-V_3), a physician assessed the patient's condition according to the established criteria and self-scoring, and together with the patient and/or parents a decision on the need of antibiotic therapy was made. The duration of follow-up for 1 patient was 10 ± 1 days.

The main efficacy criterion was: a decreased severity of symptoms of the disease, assessed according to the MSS scale, at each visit compared with the Visit 1, the dynamics of self-scoring of the symptoms of acute rhinosinusitis, dynamics of NSAID administration, the frequency of antibiotics prescription.

2.5. Sample size

The clinical study is designed to provide a reliable description of in vivo efficacy of the active use of Aqua Maris Extra Strong compared to the standard treatment only in a delayed antibiotic regimen. Depending on findings, several trial descriptive and statistical evaluations were performed so that a biometric estimate of the sample size is not required. However, in order to guarantee a sufficient sample size for data analysis, the sample size $N = 100$ was chosen. Patients were sorted in a 1: 1.

2.6. Randomization

The clinical part of the randomized study is open, without a blinding procedure. Subjects with ARS symptoms are randomized to one of two possible treatments according to the basic randomization list. Randomization was performed using the software [StatSoft is a random number generator]. Randomization was performed for each patient who signed an informed consent.

2.7. Statistical methods

In order to analyze homogeneity of groups, descriptive statistics methods were used for description of the baseline condition of the treatment and control group (for quantitative parameters — n, mean arithmetic, median, standard deviation, minimum and maximum values; for qualitative parameters — incidence and share as %). Verification of normality of data distribution in groups was performed for quantitative parameters using Shapiro-Wilk test. If the data in groups showed normal distribution according to certain parameters, the groups were compared by these parameters via Student's test for in-dependent samples. Otherwise (if the data distribution was different from normal), comparison of groups was performed according to Mann-Whitney test. For categorical parameters, the groups were compared using Pearson's chi-squared test or Fisher's exact test.

For analysis of efficacy, descriptive statistics parameters were calculated in each group (n, mean arithmetic, median, standard deviation, minimum and maximum values) for all visits in accordance with patients' examination scheme.

Analysis of dynamics of the said parameters in each group was performed via two-way analysis of variance (ANOVA) according to the following scheme: “Visit” factor is fixed (levels: visit 1… visit n); “Subjects” factor is random.

Table 1
Schedule of assessments.

V1			V2		V3					V4
Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
Treatment group Reference treatment + Aqua Maris Extra Strong										
Control group Reference treatment + isotonic saline solution										

V1 - day 0, Screening, randomization, prescription of treatment
V2 - day 3 ± 1, Status evaluation, possible prescription of antibiotics
V3 - day 5 ± 1, Evaluation of treatment efficacy, possible prescription of antibiotics
V4 - day 10 ± 1, Evaluation of treatment efficacy, end of treatment.

Results of the subsequent visits were compared against the data of visit 1 via contrast analysis using simple contrasts.

Comparison between groups in dynamics of tested parameters was performed by differences dTi = (TVisit n − TVisit 1) of assessed parameters using Mann-Whitney test.

The level of confidence for Shapiro-Wilk test was accepted equal to 0.01, and for the rest of the criteria it was accepted equal to 0.05.

The analysis of the effects of Aqua-Maris Extra Strong therapy on reducing the frequency of antibiotic use was carried out using the predictive method based on regression analysis with the use of a neural network (the probability that the analysed (dependent) variable would take on a value at given values of factors was estimated (a linear combination of factors is modelled)). In this case, regression was considered as a special case of a neural network.

The analysis was performed in software environment IBM SPSS 22.0.

3. Results

3.1. Study sample

106 persons were screened. 100 outpatients aged 6 to 11 years were included in the study (Fig. 1).

Of the 106 patients enrolled, 6 (5.6 %) were not included in the study. The reason was non-compliance with the study inclusion criteria: age non-compliance ($n = 2$) and the unwillingness of a patient and/or his/her parents to comply with the protocol requirements ($n = 4$). The remaining 100 patients were randomized to either the treatment ARS group: $n = 50$ or the control group: $n = 50$. Of the randomized patients, all 100 (100 %) underwent the necessary procedures in accordance with the study protocol and were subjected to the result analysis.

Table 2 shows the sex distribution of randomized patients in both groups: out of the 50 patients in the treatment group, 25 (50%) were

Table 2
Allocation of patients according to sex.

Gender	Treatment group (n-50)		Control group (n-50)		Chi Square	*p*-Value
	n	%	n	%		
Male	25	50.0	30	60.0	1.010	0.3149
Female	25	50.0	20	40.0		

The conclusion is drawn at the significance level of 0.05.

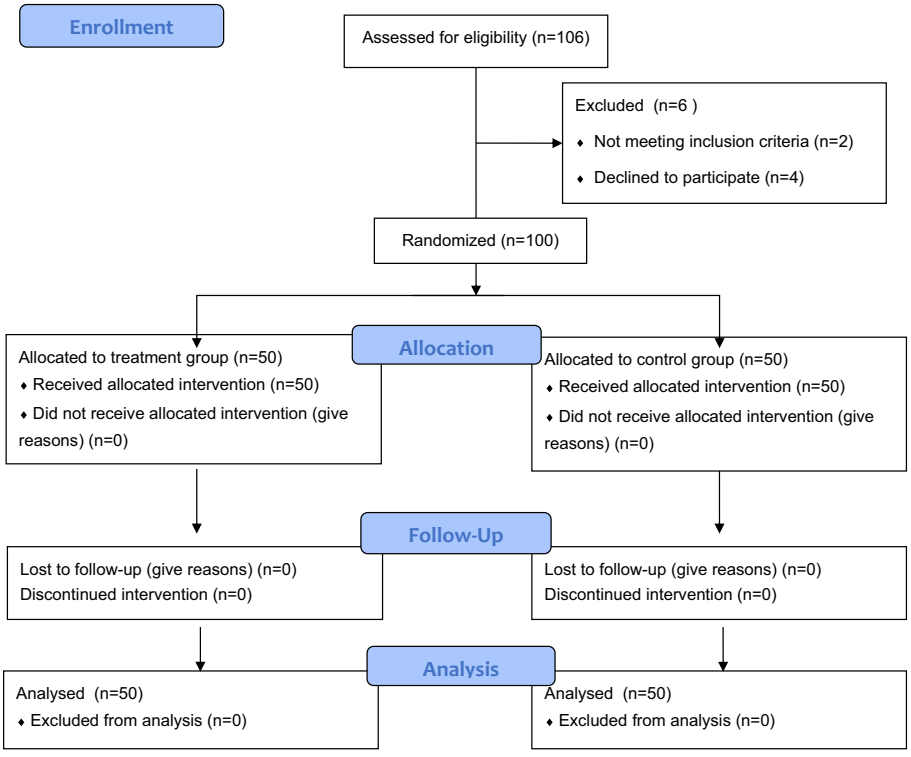

Fig. 1. Patients included in screening and randomization.

boys and 25 (50%) were girls; out of 50 patients in the control group, 30 (60%) were boys and 20 (40%) were girls).

In general, the groups were formed statistically homogeneous by gender.

Table 3 shows the distribution of patients in both groups by age: the average age of patients in the treatment group was 8.16 ± 1.72 years, in the control group — 8.12 ± 1.84 years. According to the age criterion, the groups were formed statistically homogeneous.

In general, there were no significant differences in demographic characteristics among patients in the treatment and control groups at the baseline (Day 1).

3.2. Outcomes and estimation

Typical clinical symptoms of ARS are: nasal discharge (rhinorrhea or postnasal drip), nasal congestion/obstruction, facial pain and headache. Table 4 presents the dynamics of the severity of the principal symptoms in points, evaluated by a physician using a 4-point scale in patients in the treatment and control groups.

When the physician assessed the symptom of nasal discharge (rhinorrhea), both groups showed comparable severity parameters during V1: 2.52 points in the treatment group and 2.48 in the control group. During treatment at V2, a regression in the severity of rhinorrhea in patients of both groups was observed: from 2.52 to 1.46 points in the treatment group and from 2.48 to 1.94 in the control group. At V3 there was a further regression of rhinorrhea in patients of both groups: up to 0.6 points in the treatment group and up to 1.12 points in the control group. At V4, the severity of rhinorrhea was 0.14 points in the treatment group and 0.81 in the control group. There is a tendency to a more pronounced regression of the symptom in the treatment group (Table 4).

Table 5 presents a comparative assessment between the treatment and control groups of the severity of the principal symptoms assessed by the physician in patients with ARS during treatment using the Mann-Whitney test. Comparison of the severity of rhinorrhea at V1 shows no significant differences between the groups. Assessment of the regression of the rhinorrhea symptoms between groups shows significant differences at V2 and V3 ($p < 0.05$) and non-significant differences between groups at V4 ($p > 0.05$) compared with V1.

When the physician assessed the symptom of nasal congestion, both groups showed comparable severity parameters at V1: 2.80 points in the treatment group and 2.64 points in the control group (Tables 4 and 5). During treatment at V2, a regression in the severity of nasal congestion in patients of both groups was observed: from 2.80 to 1.30 points in the treatment group and from 2.64 to 1.80 in the control group. At V3 there was a further regression of nasal congestion in patients of both groups: up to 0.54 points in the treatment group and up to 1.26 points in the control group. At V4, the severity of nasal congestion was 0.16 points in the treatment group and 0.52 points in the control group (Table 4). When comparing the regression of the nasal congestion symptoms between groups using the Mann-Whitney test, there are significant differences at V2, V3 and V4 ($p < 0.05$) (Table 5).

When the physician assessed the symptom of postnasal drip, both groups showed comparable severity parameters at V1: 2.46 points in the treatment group and 2.30 points in the control group (Tables 4 and 5).

Table 3
Allocation of patients according to age.

Parameter	Group	Statistical indicators			
		n	M ± SD	*p*-value	Homogeneity of groups[a]
Age, years	Treatment	50	8.16 ± 1.72	0.911	Homogeneous
	Control	50	8.12 ± 1.84		

[a] The conclusion is drawn at the significance level of 0.05.

During treatment at V2, a regression in the severity of postnasal drip in patients of both groups was observed: from 2.46 to 1.10 points in the treatment group and from 2.30 to 1.68 in the control group. At V3 there was a further regression of postnasal drip in patients of both groups: up to 0.36 points in the treatment group and up to 1.06 points in the control group. At V4, the severity of post-nasal drip was 0.08 points in the treatment group and 0.38 in the control group. There is a tendency to a more pronounced regression of the symptom in the treatment group (Table 4). When comparing the regression of the postnasal drip symptom between groups using the Mann-Whitney test, there are significant differences at V2, V3 and V4 ($p < 0.05$) (Table 5).

When the physician assessed the symptom of facial pain, both groups showed comparable severity parameters at V1: 1.40 points in the treatment group and 1.46 points in the control group (Tables 4 and 5). During treatment at V2, a regression in the severity of facial pain in patients of both groups was observed: from 1.40 to 0.40 points in the treatment group and from 1.46 to 0.96 in the control group. At V3 there was a further regression of facial pain in patients of both groups: up to 0.14 points in the treatment group and up to 0.54 points in the control group. At V4, the severity of facial pain was 0.06 points in the treatment group and 0.28 points in the control group (Table 4). When comparing the regression of the facial pain symptoms between groups using the Mann-Whitney test, there are significant differences at V2 ($p < 0.05$) and no significant differences at V3 and V4 ($p > 0.05$) (Table 5).

When the physician assessed the symptom of headache, both groups showed comparable severity parameters at V1: 1.76 points in the treatment group and 1.66 points in the control group (Tables 4 and 5). During treatment at V2, a regression in the severity of headache in patients of both groups was observed: from 1.76 to 0.30 points in the treatment group and from 1.66 to 1.08 points in the control group. At V3 there was a further regression of headache in patients of both groups: up to 0.12 points in the treatment group and up to 0.58 points in the control group. At V4, the severity of headache was 0.06 points in the treatment group and 0.38 points in the control group (Table 4). When comparing the regression of the headache symptoms between groups using the Mann-Whitney test, there are significant differences at V2 and V3 ($p < 0.05$) and no significant differences at V4 ($p > 0.05$) (Table 5).

Patients aged 6 to 11 years, either individually or with the help of parents, evaluated the main complaints on a daily basis in a diary using a ten-point visual-analogue scale. Since the groups were homogeneous in terms of the severity of the principal symptoms at the beginning of the study, individual differences $dTi = T_{Day2} - T_{Day1}, \ldots, T_{Day10} - T_{Day1}$ for each subject and symptom were calculated. Further comparison between groups was carried out according to the dynamics of self-assessment of the principal ARS symptoms (differences in dTi) using the Mann-Whitney test (Table 6).

According to self-assessment, there is a significant difference in the severity of rhinorrhea regression in patients of the treatment group compared with the control group, starting from the treatment day 2 (D2) and up to D8. On D9-D10, the difference in rhinorrhea symptoms was not significant (Table 6).

Dynamics of self-scoring by “nasal congestion” symptom has been studied. In patients of the treatment group, there was a more pronounced (significant) symptom regression from D2 to D9. On D10, the difference in rhinorrhea symptoms was not significant.

Comparison of the postnasal drip regression according to patient's self-assessment between groups using the Mann-Whitney test shows significant differences from D2 to D8. On D9-D10, the difference in postnasal drip symptoms was not significant.

Patient's self-assessment of facial pain shows a significant difference in symptom severity only on D2. From treatment day 3 (D3) to treatment day 10 (D10), the difference in the severity of symptoms was not significant. Self-assessment of headache severity shows a significant difference between the treatment and control groups from D2 to D6. From D7 to D10, the difference between the groups is not significant.

As you know, the presence of such a symptom as hyperthermia is an

Table 4
Severity of the on-treatment principal symptoms in points evaluated by a physician in patients with ARS during treatment.

Parameter	Visit (V)	Treatment group			Control group		
		n	Arithmetical mean	Standard deviation	n	Arithmetical mean	Standard deviation
Rhinorrhea	V 1	50	2.52	0.65	50	2.48	0.65
	V 2	50	1.46	0.79	50	1.94	0.79
	V 3	50	0.6	0.70	50	1.12	0.77
	V 4	50	0.14	0.45	50	0.37	0.81
Nasal congestion	V 1	50	2.80	0.40	50	2.64	0.56
	V 2	50	1.30	0.76	50	1.80	0.95
	V 3	50	0.54	0.68	50	1.26	0.92
	V 4	50	0.16	0.51	50	0.52	1.03
Post-nasal drip	V 1	50	2.46	0.65	50	2.30	0.71
	V 2	50	1.10	0.74	50	1.68	0.96
	V 3	50	0.36	0.60	50	1.06	0.87
	V 4	50	0.08	0.27	50	0.38	0.85
Facial pain	V 1	50	1.40	1.31	50	1.46	1.27
	V 2	50	0.40	0.81	50	0.96	1.16
	V 3	50	0.14	0.61	50	0.54	0.84
	V 4	50	0.06	0.42	50	0.28	0.81
Headache	V 1	50	1.76	1.39	50	1.66	1.30
	V 2	50	0.30	0.84	50	1.08	1.19
	V 3	50	0.12	0.59	50	0.58	0.99
	V 4	50	0.06	0.42	50	0.38	0.99

Table 5
Comparison of the dynamics of symptoms assessed by the physician in patients with ARS using the Mann-Whitney test between the groups.

Parameter	dTi	Mann–Whitney *U* test	Wilcoxon W test	Z	*p*-Value*
Nasal discharge	V1–V1	1221.5	2496.5	−0.2	0.842
	V2 – V1	858.0	2184.0	−3.203	0.001*
	V3–V1	882.5	2208.5	−2.957	0.003*
	V4 – V1	1119.5	2445.5	−1.309	0.191
Nasal congestion	V1–V1	1090.0	2365.0	−1.447	0.148
	V2 – V1	704.0	1979.0	−3.980	0.000*
	V3–V1	617.0	1892.0	−4.605	0.000*
	V4 – V1	902.5	2177.5	−2.754	0.006*
Postnasal drip	V1–V1	1100.5	2375.5	−1.14	0.254
	V2 – V1	664.0	1939.0	−4.262	0.000*
	V3–V1	612.5	1887.5	−4.623	0.000*
	V4 – V1	957.5	2232.5	−2.160	0.031*
Facial pain	V1–V1	1208.0	2483.0	−0.304	0.761
	V2 – V1	963.5	2238.5	−2.157	0.031*
	V3–V1	1104.5	2379.5	−1.050	0.294
	V4 – V1	1184.5	2459.5	−0.473	0.636
Headache	V1–V1	1203.5	2478.5	−0.329	0.742
	V2 – V1	808.5	2083.5	−3.221	0.001*
	V3–V1	967.5	2242.5	−2.019	0.044*
	V4 – V1	1036.0	2311.0	−1.521	0.128

p-conclusion is drawn at the significance level of 0.05.
* There are statistically significant differences between the groups.

important criterion for assessing the severity of the disease course and one of the main indications for patients taking non-steroidal anti-inflammatory drugs (NSAIDs). We analysed the dynamics of the duration of NSAID administration. The last drug administration date was taken into account (Table 7).

As can be seen from the presented data, the dynamics of NSAID administration in both groups was comparable.

We compared the ARS treatment outcomes between groups at V4 (Fig. 2). Out of 50 patients of the treatment group, 46 patients (92.0 %) recovered, out of 50 patients in the control group, 42 patients (84.0 %) recovered.

The difference between the groups is not significant $p = 0.357$ (> 0.05). 2 patients (4.0 %) of the treatment and 1 patient (2.0 %) of the control group continue to be ill. 1 patient of the control group had the worsening. The difference between the groups in both cases is not significant $p = 1.000$ (> 0.05).

According to the study design, a comprehensive assessment of the patient's condition was made at control visits and a decision on the need to prescribe antibiotic therapy was made (Fig. 2). Antibacterial therapy was prescribed to 2 patients (4.0 %) in the treatment group and 6 patients (12.0 %) in the control group. The difference between the groups is not significant $p = 0.269$ (> 0.05).

Taking into account the absence of a significant difference in the prescription of antibiotic therapy between the groups, we analysed the trend in the prescription of antibiotics depending on the prescription of Aqua Maris Extra Strong therapy. The analysis was carried out using neural network modelling (Fig. 3).

As can be seen from the presented figure, the prescription of AMES significantly reduces the frequency of antibiotic prescription in the treatment group compared to the control group.

3.3. Safety and tolerability

An analysis of the tolerability assessment findings showed that the treatment was well tolerated or very well tolerated in all cases. No on-treatment side effects were observed in any patient.

Table 6
Comparison between groups according to the dynamics of self-assessment of the ARS symptoms using the Mann-Whitney test.

Parameter	dTi	Mann–Whitney U test	Wilcoxon W test	Z	*p*-Value*
Rhinorrhea	D2 – D1	968.5	2243.5	−2.111	0.035*
	D3 – D1	937.0	2212.0	−2.217	0.027*
	D4 – D1	776.5	2051.5	−3.339	0.001*
	D5 – D1	774.0	2049.0	−3.332	0.001*
	D6 – D1	779.5	2054.5	−3.274	0.001*
	D7 – D1	765.0	2040.0	−3.373	0.001*
	D8 – D1	821.5	2096.5	−2.985	0.003*
	D9 – D1	1016.5	2291.5	−1.628	0.103
	D10–D1	1066.0	2341.0	−1.281	0.200
Nasal congestion	D2 – D1	836.0	2111.0	−3.079	0.002*
	D3 – D1	730.5	2005.5	−3.655	0.000*
	D4 – D1	526.0	1801.0	−5.056	0.000*
	D5 – D1	595.0	1870.0	−4.562	0.000*
	D6 – D1	606.0	1881.0	−4.476	0.000*
	D7 – D1	591.0	1866.0	−4.581	0.000*
	D8 – D1	687.0	1962.0	−3.918	0.000*
	D9 – D1	825.5	2100.5	−2.955	0.003*
	D10–D1	1013.0	2288.0	−1.654	0.098
Postnasal drip	D2 – D1	1173.5	2448.5	−0.579	0.562
	D3 – D1	940.0	2215.0	−2.178	0.029*
	D4 – D1	838.5	2113.5	−2.877	0.004*
	D5 – D1	801.5	2076.5	−3.139	0.002*
	D6 – D1	784.0	2059.0	−3.25	0.001*
	D7 – D1	714.5	1989.5	−3.736	0.000*
	D8 – D1	950.5	2225.5	−2.078	0.038*
	D9 – D1	1047.0	2322.0	−1.411	0.158
	D10–D1	1149.0	2424.0	−0.702	0.483
Facial pain	D2 – D1	938.0	2213.0	−2.425	0.015*
	D3 – D1	1023.5	2298.5	−1.632	0.103
	D4 – D1	997.0	2272.0	−1.794	0.073
	D5 – D1	1047.5	2322.5	−1.431	0.152
	D6 – D1	1046.0	2321.0	−1.434	0.152
	D7 – D1	1094.0	2369.0	−1.098	0.272
	D8 – D1	1188.0	2463.0	−0.436	0.663
	D9 – D1	1236.5	2511.5	−0.095	0.924
	D10–D1	1237.5	2512.5	−0.088	0.930
Headache	D2 – D1	1121.5	2396.5	−0.928	0.353
	D3 – D1	826.5	2101.5	−2.987	0.003*
	D4 – D1	845.5	2120.5	−2.825	0.005*
	D5 – D1	847.5	2122.5	−2.808	0.005*
	D6 – D1	971.5	2246.5	−1.938	0.053*
	D7 – D1	1050.5	2325.5	−1.389	0.165
	D8 – D1	1128.0	2403.0	−0.848	0.396
	D9 – D1	1156.5	2431.5	−0.65	0.516
	D10–D1	1170.5	2445.5	−0.553	0.580

D is a day. *P*-conclusion is drawn at the significance level of 0.05.
* There are statistically significant differences between the groups.

4. Discussion

Acute bacterial rhinosinusitis (ABRS) occurs in only about 0.5 % to 5 % of all ARS cases [2,3]. It is this number of patients that antibiotic therapy is indicated to. However, in ARS, antibiotics are prescribed 4–9 times more often than recommended [6]. In terms of using a delayed antibiotic strategy, initial treatment should be highly effective, especially with regard to the "core" or "key" symptoms of ARS — nasal congestion and mucopurulent discharge from the nose [7]. With insufficient efficacy of initial therapy and during repeated examination, the need to prescribe antibacterial drugs is always considered both among doctors and the patients themselves or their parents [6].

According to the design, our study included patients with diagnostic criteria for acute non-bacterial rhinosinusitis. The severity of symptoms between groups on Day 1 was comparable ($p > 0.05$). The study demonstrated that the use of hypertonic seawater solution in addition to standard ARS therapy has a proven therapeutic effect already in the first days of treatment.

According to the physician assessment of the core or key symptoms of ARS, the rhinorrhea regression between groups shows significant differences at V2 and V3 ($p < 0.05$) and non-significant differences between groups at V4 ($p > 0.05$) compared with V1. When comparing the regression of the nasal congestion symptoms and postnasal drip between groups, there are significant differences at V2, V3 and V4 ($p < 0.05$).

There are also significant differences in the patient self-assessment of the intensity of rhinorrhea and nasal congestion already on Day 2 (D2) and postnasal drip on Day 3 (D3) of treatment ($p < 0.05$). Significant differences persisted up to D9-D10, i.e. to the end of treatment, when the difference in symptom intensity scores was not significant ($p > 0.05$).

Thus, when using irrigation therapy with a hypertonic seawater solution in patients of the treatment group, compared with those in the control group, there was a significant "therapeutic gain" in terms of regression of the core or key ARS symptoms (rhinorrhea, nasal congestion and postnasal drip) already in the first days of treatment, when the decision to delay the antibacterial drug prescription is made.

Our results reflect those showing a proven clinical benefit from the use of isotonic saline solution for the treatment of acute respiratory infections [13–15]. However, in the context of our study, the poor data showing that irrigation therapy of ARS with isotonic solution in children improves nasal breathing and reduces the amount of nasal discharge are more valuable. The indicators of the self-assessment questionnaire for the quality of life are confirmed by the examination data: a decrease in mucosal oedema and indicators of peak nasal expiratory flow [20,21]. This clinical effect confirms previously obtained data on the

Table 7
Dynamics of systemic NSAID administration.

Parameter	Group	n	Mean	Mann–Whitney U test	Wilcoxon W test	Z	*p*-Value
NSAID administration, days	Treatment	50	2.34	1157.500	2432.500	−0.650	0.516
	Control	50	2.54				

p-conclusion is drawn at the significance level of 0.05.

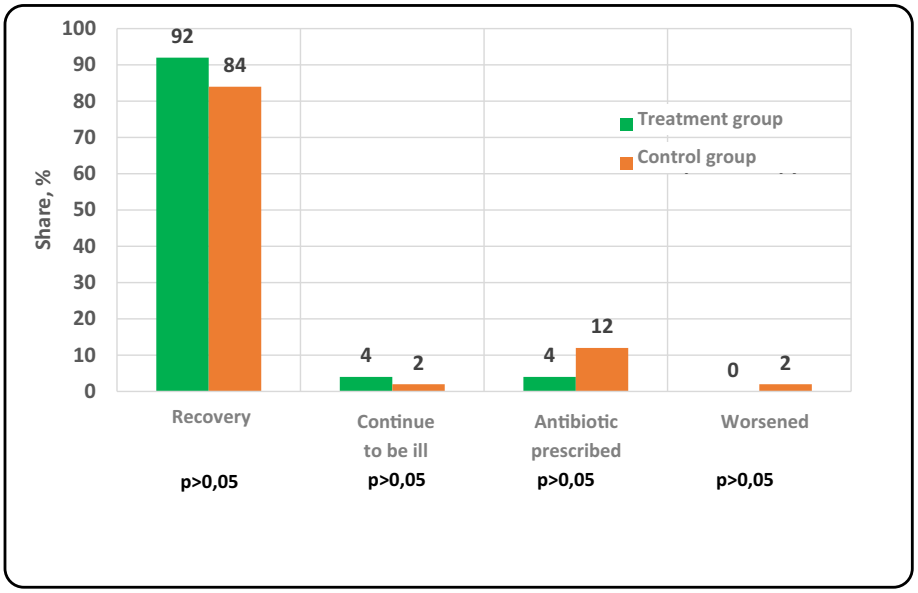

Fig. 2. Treatment results at V4.

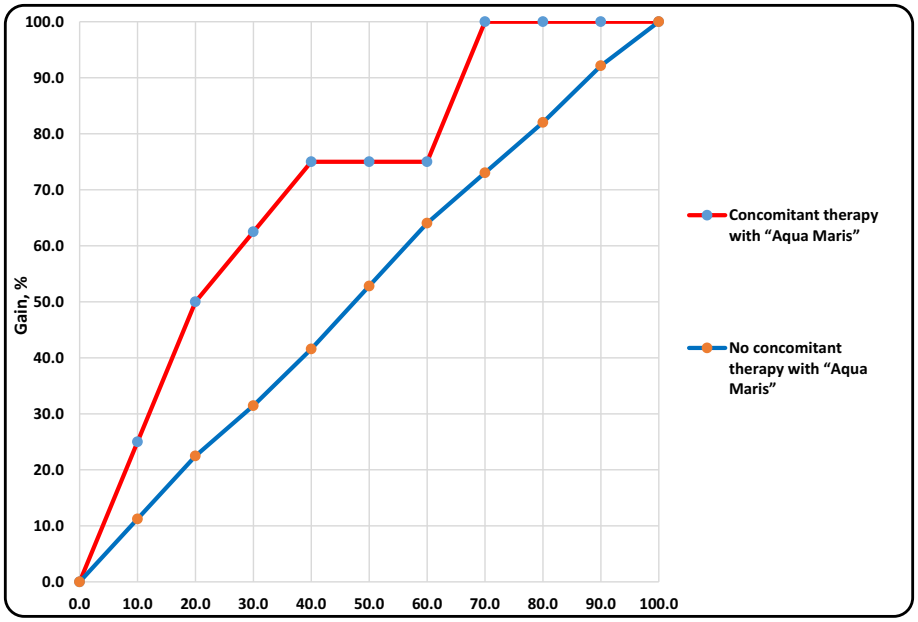

Fig. 3. Analysis of the prescription of “Aqua Maris Extra Strong” therapy on reducing the frequency of antibiotic use.

improvement of the rheological properties of nasal mucus and stimulation of mucociliary clearance under the influence of isotonic seawater [16–18]. In our study, these effects are potentiated by the additional use of the BNO 1012 phytoextract, which has similar properties [7].

One of the important symptoms of ARS is pain, both headache and facial pain. In ARS, the pain syndrome is mainly associated with the toxic effect of viruses, swelling of the mucous membrane of the paranasal sinuses and blockade of fistulas. In our study, both groups demonstrated comparable indicators of facial pain and headache in terms of severity, both in the physician assessment of symptoms at V1, and the patient self-assessment of symptoms on D1 ($p > 0.05$). When the physician compares the regression of the facial pain, there are significant differences at V2 ($p < 0.05$) and the absence of significant differences at V3 and V4 ($p > 0.05$); when it comes to headache, there are

significant differences at V2 and V3 ($p < 0.05$) and no significant differences at V4 ($p > 0.05$).

Patient's self-assessment of facial pain shows a significant difference in symptom severity on D2 ($p < 0.05$). From treatment day 3 (D3) to treatment day 10 (D10), the difference in the severity of symptoms was not significant ($p > 0.05$). Self-assessment of headache severity shows a significant difference between the treatment and control groups from D2 to D6. From D7 to D10, the difference between the groups is not significant.

Less pronounced dynamics of reduction of facial pain and headache compared to other ARS symptoms can be explained by the minimal effect of endonasal irrigation on the state of the mucous membrane of the paranasal sinuses in ARS. The conducted studies did not show a statistically significant improvement in the radiographic index of the paranasal sinuses [20].

Thus, an important and interesting conclusion of the study is that the use of hypertonic seawater solution Aqua Maris Extra Strong in patients with ARS leads to a pronounced, significant regression of such important symptoms as rhinorrhea, postnasal drip, nasal congestion, facial pain and headache already by the first control (V2) visit of the patient ($p < 0.005$).

As you know, the presence of pain in combination with hyperthermia increases the likelihood of irrational prescription of antibacterial drugs. In such cases, the prescription of non-steroidal anti-inflammatory drugs is recommended. The study showed that in patients of the treatment and control groups there is no significant difference in the duration of NSAID administration. This allows us to conclude that the results obtained in the dynamics of ARS symptoms can be explained by the clinical effects of Aqua Maris Extra Strong.

According to the design, our study did not include patients with diagnostic criteria for acute bacterial RS requiring immediate antibiotic therapy. The decision on prescription of antibiotics was made after evaluation the dynamics of symptom regression at V2–3. In such cases, antibiotic therapy was considered rational, since the treatment prescribed at V1 did not show sufficient efficacy. Antibacterial therapy was prescribed to 2 out of 50 patients (4.0 %) in the treatment group and 6 out of 50 patients (12.0 %) in the control group. This low frequency of prescription is in line with current recommendations for antibiotic therapy for ARS [2,26]. There is a tendency to reduce the number of prescriptions in the treatment group, but the difference between the groups is not significant ($p > 0.05$). The small sample size of patients did not allow statistically significant conclusions to be drawn using standard statistical methods. Therefore, an analysis of the tendency in prescribing antibiotics was carried out using neural network modelling. It was shown that the prescription of Aqua Maris Extra Strong significantly reduces the frequency of antibiotic prescriptions in the treatment group compared to the control group.

Thus, an important conclusion of the study is that the use of hypertonic seawater solution in patients with ARS reduces the need for antibiotic therapy as part of the technology of delayed antibiotic prescription. However, according to literature data, irrational antibacterial therapy is prescribed much more often than necessary [6]. The proven high efficacy of ARS treatment in terms of pronounced regression of symptoms in the first days will make it possible to more widely implement the strategy of delayed antibiotic prescription and significantly reduce the number of irrational prescriptions of antibacterial drugs at the first patient visit.

The design involved a comparative study that did not allow for a placebo control. However, the comparison was made between groups treated according to clinical guidelines. So the treatment effect can be considered the same in the groups [2,26]. In this regard, all the differences between treatment results can be attributed to the clinical effects of the hypertonic seawater solution Aqua Maris Extra Strong, since the group characteristics were comparable.

5. Conclusions

It has been shown that the addition of a hypertonic seawater solution to the standard symptomatic therapy with BNO 1012 for the treatment of acute rhinosinusitis provides a significant clinical effect in the first days of treatment. Clinical symptoms of the disease are significantly reduced in comparison with the control. The therapeutic effect in the first days of treatment reduces the need for antibiotics. The inclusion of the drug in the treatment regimen may be recommended for patients with ARS as part of a strategy for delayed antibiotic prescription.

The prospect of further studies is to study the drug efficacy in patients with bacterial rhinosinusitis.

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