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Effects of Topical Polymyxin Neomycin Hydrocortison in Patients with Non-Allergic Rhinitis, a Randomized Clinical Trial

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ABSTRACT

Background: Bacterial infection is involved in the pathogenesis of inflammatory non-allergic rhinitis (NAR), and a broad-spectrum antibiotic should reduce the severity of the disease by eliminating the mucosal biofilm. The purpose of this study is to assess the efficacy of a topical mixture of polymyxin, neomycin, and hydrocortisone in patients with NAR.

Methods: This double-blind phase 3 randomized clinical trial was conducted on 90 patients with non-allergic rhinitis (NAR) in Mashhad, Iran. The subjects experienced symptoms for more than two weeks, and the pretrial course of topical corticosteroids was ineffective. Patients were randomly assigned to treatment groups receiving polymyxin NH, hydrocortisone, or saline. The drug was administered as nasal drops three times daily for a treatment course of two weeks, and the containers were identical. The primary outcome was nasal obstruction.

Results: The pretrial comparison showed no significant difference between groups in terms of clinical findings. However, after the trial, nasal obstruction, as the primary outcome, significantly decreased from 20 subjects (66%) to 7 subjects (23%) in the Polymyxin NH group, along with other secondary outcomes, including palatal itching (56% to 23%), sneezing (76% to 40%), mucosal inflammation (100% to 75%), post-nasal drip (PND) (96% to 63%), and concha swelling (96% to 73%). In the other groups, sneezing was the only significant improvement observed in the saline group. Cytology of nasal discharge showed a reduction in nasal neutrophil counts in the Polymyxin NH group (68±16.7% to 46±27.6%) compared to the hydrocortisone and saline-treated groups.

Conclusion: Topical intranasal polymyxin NH is effective in treating patients with non-allergic rhinitis.

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Introduction

Non-allergic rhinitis (NAR) is a type of chronic rhinitis characterized by nasal mucosal inflammation, rhinorrhea, nasal obstruction, sneezing, nasal itching, and post-nasal drip (PND) in the absence of systemic allergy and infection symptoms (1). It is a prevalent condition that affects approximately 200 million people worldwide (2). NAR is clinically diagnosed when the skin prick test and serum-specific immunoglobulin E (IgE) antibody assay are negative (3, 4). Factors such as airway hyperreactivity, hormonal imbalances, medications, and occupational exposure can all contribute to the etiology of NAR through immunological mechanisms (3). Based on this, the European Academy of Allergy and Clinical Immunology has classified NAR into several subgroups: senile rhinitis, occupational rhinitis, gustatory rhinitis, drug-induced rhinitis, hormonal rhinitis, and idiopathic rhinitis (4). Furthermore, NAR can be categorized as non-inflammatory or inflammatory. Non-inflammatory (neurogenic) NAR results from vasomotor dysfunction, whereas inflammatory NAR (eosinophilic or non-eosinophilic) is characterized by an increase in the number of inflammatory cells in the nasal mucosa. Typical inflammatory cells found in the nasal mucosa of NAR patients include eosinophils, neutrophils, and mast cells (5). In this context, NAR with eosinophilia syndrome (NARES) is the most common type of inflammatory NAR, defined cytologically by more than 25% eosinophils (1, 6, 7). Patients with NARES tend to experience more severe nasal symptoms compared to those with vasomotor rhinitis (6).

Although NAR is defined as a non-infectious rhinitis, some researchers believe that certain cases of idiopathic NAR may be caused by undiagnosed bacterial infections of the nasal mucosa (8). A nasal bacterial infection can affect nasal epithelial cells and lead to chemokine-triggered leukocyte infiltration (9). As a result, inflammatory cells such as neutrophils and eosinophils infiltrate the nasal mucosa and trigger inflammation (10). The European Position Paper on Rhino-sinusitis and Nasal Polyps (EPOS 2020) has introduced corticosteroids, antibiotics, and surgery as the mainstays of treatment for rhinosinusitis (11). In this report, barrier disruption is one of the pathological mechanisms that has gained attention, with three types of immune defensive responses identified. The third response (type 3) is related to bacteria. Systemic antibiotics are the primary treatment for this pathology; however, the formation of biofilm may interfere with the eradication of bacteria. According to the studies referenced in EPOS 2020, the authors of this guideline consider topical antibiotic therapy to be questionable. We believe that further research is needed to elucidate the efficacy of topical antibiotic therapy for chronic rhinosinusitis, particularly since many broad-spectrum antibiotics with minimal mucosal absorption and low side effects have not yet been used. A potent topical antibiotic available in our region is polymyxin NH ear drops, which is a topical corticosteroid-antibiotic medication containing polymyxin B sulfate, neomycin, and hydrocortisone (12). Neomycin is a broad-spectrum antibiotic effective against gram-positive and gram-negative bacteria, while polymyxin B is effective against a wide range of gram-negative bacteria (12). Due to its low absorption from the nasal epithelium and potent effect on a diverse range of bacteria, polymyxin NH is an appropriate candidate for evaluating our hypothesis. Consequently, this study aimed to assess the efficacy of topical polymyxin NH administration in patients suffering from NAR. We also investigated the effect of polymyxin NH on leukocyte infiltration into the nasal epithelial layer.

Materials and Methods

Ethical considerations

The local ethics committee approved the study protocol for the current investigation (approved number: IR.IAU.MSHD.REC.1398.151), and it was carried out in accordance with the Helsinki Declaration on the Treatment of Human Subjects (13). The study's objectives and the characteristics of the medications were explained to the patients, who then provided written informed consent. We are also committed to maintaining patient confidentiality and not charging them any additional fees.

Sampling

This double-blind randomized clinical trial included 90 new patients suffering from non-allergic rhinitis (NAR), with or without polyposis, who had been treated for more than 2 weeks with inhaled nasal corticosteroids. The study took place at a respiratory clinic in Mashhad, Iran, between July 2017 and February 2018. Permuted block randomization was conducted to ensure a similar distribution of samples into three groups. The inclusion criteria were as follows: 1) a history of non-seasonal nasal allergy (rhinorrhea, nasal obstruction, sneezing, and palatal itching); 2) the absence of relapse and remission periods; 3) the absence of fever, bleeding, unilateral involvement, facial deformity, and severe headache; 4) resistance to topical glucocorticoids during the pretrial period; 5) at least one week having passed since the last respiratory infection; and 6) the possibility of patient follow-up. Patients with systemic diseases, nasal anatomical disorders, drug sensitivities, and those who responded to corticosteroids (i.e., those with allergic rhinitis) were excluded from the study.

Experimental groups

Ninety NAR patients were randomly assigned to 15 blocks, each containing three groups with two subjects per group. The final list was created using the research randomizer® website, and each subject received a unique code. The Polymyxin NH group received a single drop of polymyxin NH (polymyxin B sulfate 10,000 U/ml + neomycin sulfate 5 mg/ml + hydrocortisone 10 mg/ml). The second group (first control) received hydrocortisone (2 mg/ml) to evaluate the effect of topical corticosteroids, which are included in Polymyxin NH drops. The third group (second control) received an equal volume of 6.7 g/L sodium chloride to evaluate the rinsing effect of the diluent, considering a mechanical etiology. The drugs were administered in the nasal cavity three times per day for two weeks. The drug packages were completely similar to the polymyxin NH drops, except for the unique code. The physician and clinic staff were unaware of the group assignments, and a staff member in the pharmacy opened the envelope for each subject to obtain the required drug.

Study Protocol

The primary outcome was nasal obstruction, while other nasal symptoms, physical examination findings, and the frequency of inflammatory cells, including their classification, were considered secondary outcomes. The clinical examination findings, along with the patient's past medical history and demographic information, were documented in checklists. The subjective clinical findings were graded using a visual analogue scale for each symptom. Afterward, each participant's nasal mucosa was swabbed and placed in a PBS-filled tube. The tissues were then stained with Giemsa stain to detect inflammatory cells. In addition to the frequency of inflammatory cells, subjects were classified as eosinophilic if the eosinophil count was greater than 25% and

neutrophilic if the neutrophil count was greater than 65%.

Statistical analysis

IBM Corp. SPSS v. 26.0 (USA) was used to analyze the quantitative data, which was expressed as mean ± SD or percentages. After determining the normality of the quantitative data distribution using the Kolmogorov-Smirnov test, the Kruskal-Wallis, Chi-Square, and Fisher Exact tests were employed for multiple comparisons between groups. Furthermore, the Friedman, McNemar, and Wilcoxon signed-rank tests were used to compare each group before and after the treatments. P-values less than 0.05 were considered statistically significant.

Results

Demographic information

Ninety subjects suffering from non-allergic rhinitis were included in this study (43 males [48.3%] and 46 females [51.7%]; one subject was lost to follow-up). The average age was 38.9 ± 14.2 years. In terms of gender distribution, average age, and occupational profiles, no statistical differences were found among the three groups (Table 1).

Clinical Signs and Nasal Symptoms

Nasal obstruction, rhinorrhea, and sneezing were the most frequent symptoms, which did not reveal significant differences between groups before the trial (Table 2). However, nasal obstruction, palatal itching, and sneezing were significantly reduced by polymyxin NH (Table 2). Treatment with hydrocortisone and sodium chloride did not show significant changes after the trial, except for a reduction in sneezing with sodium chloride (Table 2).

Physical examinations showed a high frequency of mucosal inflammation, erythema, post-nasal drip, and swelling of the conchae before the trial (Table 3); however, the differences between groups were not significant. These three physical findings decreased significantly in the polymyxin NH group, and the frequency of concha swelling was significantly reduced compared to the other groups (Table 3). Subsequent comparisons between the two groups using the Bonferroni test demonstrated a significant difference in concha swelling between the polymyxin NH and hydrocortisone groups ($P<0.0001$), and a significant difference in mucosal inflammation was observed between the hydrocortisone and saline groups ($P<0.01$). Nevertheless, no significant improvement in sneezing, nasal obstruction, or post-nasal drip (PND) was observed after hydrocortisone therapy. The cobblestone appearance of the posterior pharynx, nasal secretion colors, and nasal crusting did not show statistically significant differences among the three groups at baseline or after treatment (Table 3).

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Nasal Leukocyte Counts

Nasal swabs were able to provide sufficient cells to assess inflammatory cells in 45 subjects (50%). Pre-trial assessment of nasal leukocyte counts showed a significant difference between the polymyxin NH group and the two other groups (Table 4; $P<0.01$). To eliminate the effects of pretreatment heterogeneity on post-treatment leukocyte count comparisons, ANOVA statistical analysis was employed. The results revealed a significant difference among the groups following treatment, and subsequent intergroup comparisons indicated that this difference existed between the polymyxin NH and saline groups (Table 4; $P< 0.05$).

Table 1. The average age and gender distribution of patients in experimental groups.

Group	Polymyxin NH Mean ± SD	Hydrocortisone Mean ± SD	Saline Mean ± SD	P
Mean Age	37.13 ± 12.76	43.28 ± 15.04	36.45 ± 14.42	0.14
Male	11 (36.7%)	13 (44.8%)	19 (63.3%)	0.1
Female	19 (63.3%)	16 (55.2%)	11 (36.7%)	

ANOVA test (age) and Chi-square test (gender) for multiple comparisons of experimental groups.

Table 2. Clinical symptoms of non-allergic rhinitis patients before and after treatment.

Groups		Polymyxin NH		Hydrocortisone		Saline		P^K
		Mean ± SD	P^F	Mean ± SD	P^F	Mean ± SD	P^F	
Rhinorrhea	Before	25 (83.4%)	0.9	23 (76.7%)	0.13	22 (73.7%)	0.16	0.8
	After	14 (46.6%)		17 (56.4%)		15 (50.0%)		0.4
Nasal Obstruction	Before	20 (66.7%)	0.01	25 (83.4%)	0.22	17 (56.6%)	0.63	0.71
	After	7 (23.3%)		15 (51.8%)		16 (53.4%)		0.02
Palate Itching	Before	17 (56.75%)	0.03	11 (36.6%)	0.3	9 (31.1%)	0.6	0.09
	After	7 (23.4%)		8 (26.6%)		9 (30.0%)		0.3
Sneezing	Before	23 (76.6%)	0.01	19 (63.3%)	0.09	18 (60.0%)	0.01	0.11
	After	12 (40.0%)		13 (43.3%)		12 (40.0%)		0.9

[F]) Friedman test compares patients' symptoms before and after therapy.
[K]) Kruskal-Wallis test for multiple comparisons of experimental groups before and after treatment.

Table 3. Comparison of nasal and pharynx symptoms of patients with non-allergic rhinitis before and after treatment.

Groups		Polymyxin NH [A]		Hydrocortisone [B]		Saline [C]		$P^{K, F}$
		Mean ± SD	$P^{F, M}$	Mean ± SD	$P^{F, M}$	Mean ± SD	$P^{F, M}$	
Mucosal Inflammation	Before	29 (100%)	0.04*	21 (70%)	0.15	26 (86.7%)	0.16	0.19
	After	21 (75.0%)		23 (79.3%)		19 (67.8%)		0.03* P^{BC}
PND	Before	29 (96.7%)	0.001*	24 (80.0%)	0.8	23 (76.6%)	0.09	0.18
	After	19 (63.3%)		24 (82.7%)		24 (85.8%)		0.4
Cobblestone	Before	1 (3.3/%)	0.99	3 (10.0%)	0.99	1 (3.3%)	0.99	0.6
	After	0 (0.0%)		4 (13.8%)		1 (3.6%)		0.08
Crust	Before	0 (0.0%)	0.99	2 (6.7%)	0.99	3 (10.3%)	0.99	0.3
	After	0 (0.0%)		1 (3.4 %)		2 (7.1%)		0.32
Conchae swelling	Before	29 (96.7%)	0.0001*	30 (100%)	0.76	26 (86.7%)	0.1	0.09
	After	21 (73.4%)		29 (100%)		23 (82.1%)		0.02* P^{AB}

[F, M]) Friedman test (inflammation, PND, and conchae edema) and McNemar test (cobblestone and crust) compare patients' symptoms before and after therapy.
[K, F]) Kruskal-Wallis test (inflammation, PND, and conchae edema) and fisher exact test (cobblestone and crust) for multiple comparisons of experimental groups before and after treatment.

Table 4. Leukocyte counts before and after treatment in patients with non-allergic rhinitis.

Scale		Polymyxin NH		Hydrocortisone		Saline		P^{K}
		Mean ± SD	P^{W}	Mean ± SD	P^{W}	Mean ± SD	P^{W}	
Leukocytes Counts	Before	7050±3068	0.08	4181±2676‡	0.42	4375±3505‡	0.0001	0.007* P^{AB}, P^{BC}
	After	4045±2581		7700±6781		12363±1948		0.88
Neutrophils (%)	Before	68±16.7	0.01	51±38.4	0.6	39±31.3‡	0.47	0.01*
	After	46±27.6		56±29.5		49±31.3		0.9
Eosinophils (%)	Before	32±16.7	0.09	40±37.7	0.67	47±33.7	0.84	0.15
	After	53±27.6		44±29.2		49±30.9		0.44

However, post-trial results showed a significant decrease in the total number of nasal leukocytes following polymyxin NH treatment (Table 4; $P < 0.001$). In contrast, the number of leukocytes in the hydrocortisone and saline groups increased at the end of treatment compared to pretreatment.

Classification of Inflammatory Cells

The frequency of eosinophils ranged from 16 to 25% of the inflammatory cells in the groups (Table 4). Kruskal-Wallis test results revealed no statistically significant difference in nasal eosinophil counts before and after the treatment, indicating that the three experimental groups were homogeneous. Furthermore, the Wilcoxon test results showed no significant difference in post-treatment eosinophil counts in any group compared to pretreatment (Table 4). The frequency of neutrophils was between 20 to 45% of the inflammatory cells in the groups (Table 4). The Kruskal-Wallis test revealed a significant difference across the three experimental groups in pretreatment nasal neutrophil counts ($P<0.01$), but no difference after treatment (Table 4). The Bonferroni test showed the pretreatment difference between the polymyxin NH group and the two other groups ($P<0.05$). Nevertheless, covariance analysis revealed no significant differences between the groups after the treatments. The Wilcoxon test, however, exhibited a significant decrease in nasal neutrophil counts following polymyxin NH treatment compared to baseline (Table 4; $P<0.01$). Comparison of different groups according to eosinophilic and neutrophilic classifications showed no significant difference between groups, except for a high frequency of palatal itching in the eosinophilic group (Supplementary file 2). Eosinophilic subjects remained eosinophilic in 78% of cases after the treatment, and the treatment did not affect the pattern of inflammatory cells after the treatment.

Side effects

A burning sensation after the instillation of Polymyxin NH drops was reported in 56% of subjects, which lasted for 15±4.5 seconds. Bleeding after usage was reported in one subject.

Discussion

In this clinical trial, all new chronic rhinosinusitis subjects were enrolled in the pre-trial phase. Based on their history and a course of inhaled corticosteroids, allergic subjects were filtered out and excluded from the study. The remaining subjects were randomly divided into three groups: Polymyxin NH, hydrocortisone (positive control), and sodium chloride (negative control). The results of the study showed significant improvement in all clinical symptoms, including rhinorrhea, nasal obstruction, sneezing, and palatal itching, with Polymyxin NH administration. Physical examinations demonstrated significant improvement in mucosal erythema, post-nasal drip, and concha swelling. Cytological evaluation of nasal discharge revealed a significant reduction in total leukocytes and specifically neutrophils with Polymyxin NH. The basis of this study was grounded in several bacteriological studies on the microbiome of the nasal mucosa and the trend toward resistant bacterial transformation (14), as well as the special environmental milieu, such as biofilm formation, which makes the eradication of bacteria difficult (11). However, some researchers believe that bacterial infections of the nasal mucosa may trigger an immune response via the release of chemokines from the nasal epithelium (8, 15), and simultaneous impairment of muco-ciliary clearance induced by allergy may predispose individuals to superimposed bacterial infections (16). As a result, if a nasal bacterial infection is implicated in the pathogenesis of non-allergic rhinitis (NAR), intranasal antibiotic therapy may improve symptoms of the disease. In this context, intranasal topical antibiotic treatment could deliver high concentrations of active medications

directly to the nasal bacterial biofilm, which cannot be achieved systemically without antibiotic toxicity. Analysis of the other groups, including hydrocortisone (used to evaluate the effect of hydrocortisone in the Polymyxin NH mixture) and 0.67% NaCl (used to evaluate the effect of discharge removal by saline), showed that saline could significantly reduce sneezing, whereas this effect was not observed in the hydrocortisone group. However, there was no significant difference in the prevalence of sneezing between the Polymyxin NH and saline groups. As a result, the effects of saline on sneezing in patients with NAR appear to be primarily due to washing the nasal mucosa. Saline nasal washing may have indirectly decreased the intensity of the immune response by lowering bacterial populations in the nasal mucosa. However, determining the most important mechanism requires further investigation. None of the treatments, however, were beneficial in lightening the color of nasal secretions, cobblestones, or removing nasal crusts. The results regarding this item are unreliable because the sample size was insufficient, and only a small number of subjects (five subjects) had nasal crusts or cobblestones at the beginning of the study. According to pharyngeal examinations, post-nasal drip (PND) was reduced in the Polymyxin NH-treated subjects, but not in those treated with hydrocortisone or nasal saline. The cytological assessment showed that total leukocyte and neutrophil counts in the nasal secretions of patients treated with Polymyxin NH decreased following treatment. Furthermore, the Polymyxin NH-treated group had significantly lower post-treatment leukocyte and neutrophil counts than the other groups. However, these treatments did not affect the eosinophil population in nasal secretions. EPOS 2020 considered topical antibiotic therapy to be questionable and did not recommend it as a useful treatment due to some unsuccessful studies, such as Sykes et al. (17), who showed that reducing nasal inflammation and congestion with dexamethasone and tramazoline is sufficient to alleviate disease symptoms without the need for topical antibiotics. In another double-blind trial, Desrosiers and colleagues (18) evaluated the efficacy of a thrice-daily nebulized topical saline-tobramycin solution for four weeks in 20 patients with chronic rhinosinusitis refractory to topical antibiotics and surgical therapy. The results of this study showed that aerosol therapy improves patient symptoms, but tobramycin appears to provide minimal benefit. The findings of the present study contradict these results regarding the efficacy of antibiotic treatment in alleviating NAR symptoms. One explanation for this difference could be the co-administration of two broad-spectrum antibiotics in the present study. However, one of the limitations of these studies was the lack of direct culture of the nasal mucosa. Barazi et al. (19) correspondingly compared the efficacy of topical intranasal ciprofloxacin in saline (twice daily) to oral amoxicillin-clavulanic acid in the treatment of 99 children with chronic rhinosinusitis for four weeks. They discovered that while both topical and oral antibiotics could significantly reduce disease symptoms compared to pretreatment, patients treated with topical antibiotics had significantly greater improvement in total symptom scores ($P<0.01$) compared to those receiving oral antibiotics. They concluded that intranasal antibiotics were as effective as oral antibiotics in treating chronic rhinosinusitis in children. Recently, Mao et al shwed that intranasal delivery of neomycin induced expression of multiple interferon-stimulated genes — through mechanisms independent of the drug's antibacterial effects. Activation of these genes is an important part of containing viral infections. The team now demonstrates that activation of these genes in mice has dose-dependent benefits for both preventing and treating infection with SARS-CoV-2 (multiple variants) and influenza A viruses: Whether neomycin was exert its effect through an antibacterial action, is a matter of debate (20). The most frequent side effect of

Polymyxin NH was a burning sensation after the instillation of the drops inside the nostrils. This side effect is related to the special formulation of the drops for ear use. Therefore, improving the formulation for nasal use may make the application of this drug easier and enhance drug penetration. We believe that the most active ingredients of this drug are polymyxin and neomycin, and hydrocortisone could be eliminated from future formulations.

Conclusion

According to the findings of this study, two weeks of intranasal administration of Polymyxin NH drops, which contain polymyxin B sulfate and neomycin sulfate, could effectively improve symptoms of non-allergic rhinitis (NAR), including nasal obstruction, sneezing, post-nasal drip (PND), inflammation of the nasal mucosa, and edema of the nasal conchae. Additionally, this treatment also decreased total leukocyte and neutrophil counts in nasal secretions.

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Ethics approval and consent to participate

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Conflict of interest

The authors have no conflict of interest.

References

1. Meng Y, Wang C, Zhang L. Diagnosis and treatment of non-allergic rhinitis: focus on immunologic mechanisms. *Expert Rev Clin Immunol* 2021;**17**(1):51-62.
2. De Corso E, Seccia V, Ottaviano G, et al. Clinical evidence of type 2 inflammation in non-allergic rhinitis with eosinophilia syndrome: a systematic review. *Curr Allergy Asthma Rep* 2022;1-14.
3. Van Gerven L, Boeckxstaens G, Hellings P. Update on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. *Rhinology* 2012; **50**(3):227-35.
4. Hellings PW, Klimek L, Cingi C, et al. Non-allergic rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 2017; **72**(11):1657-65.
5. Del Giudice AM, Barbara M, Russo GM, et al. Cell-mediated non-allergic rhinitis in children. *Intl J Ped Otorhinolaryngol* 2012; **76**(12):1741-5.
6. Ellis AK, Keith PK. Nonallergic rhinitis with eosinophilia syndrome. *Cur allergy Asthma Rep* 2006; **6**(3):215-20.
7. Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: a practice parameter update. *J Allergy Clin Immunol* 2020; **146**(4):721-67.
8. Bousquet J, Fokkens W, Burney P, et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. *Allergy* 2008; **63**(7):842-53.
9. Cole AL, Muthukrishnan G, Chong C, et al. Host innate inflammatory factors and staphylococcal protein A influence the duration of human *Staphylococcus aureus* nasal carriage. *Muc Immunol* 2016; **9**(6):1537-48.
10. Delemarre T, Bochner BS, Simon HU, et al. Neutrophils and eosinophils in chronic rhinosinusitis. *J allergy Clin Immunol* 2021; **148**(2):327-35.
11. Fokkens WJ, Lund VJ, Hopkins C, et al. European position paper on rhinosinusitis and

nasal polyps 2020. *Rhinology*. 2020 Feb 20;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600. PMID: 32077450.
12. Amani S, Moeini M. Comparison of boric acid and combination drug of polymyxin, neomycin and hydrocortisone (polymyxin NH) in the treatment of acute otitis externa. *J Clin Dia Res* 2016; **10**(7):MC01.
13. Association WM. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* 2013; **310**(20):2191-4.
14. Doyle WJ, Gentile DA, Skoner DP. Viral and bacterial rhinitis. *Clin Allergy Immunol* 2007; **19**:177-95.
15. Erhan E, Külahli I, Kandemir O, et al Comparison of topical silver nitrate and flunisolide treatment in patients with idiopathic non-allergic rhinitis. *Tokai J Exp Clin Med* 1996; **21**(2):103-11.
16. Shah R, McGrath KG, editors. Nonallergic rhinitis. Allergy and Asthma Proceedings; 2012: OceanSide Publications.
17. Sykes D, Chan K, Wilson R, et al. Relative importance of antibiotic and improved clearance in topical treatment of chronic mucopurulent rhinosinusitis: a controlled study. *Lancet* 1986; **328**(8503):359-60.
18. Desrosiers MY, Salas-Prato M. Treatment of chronic rhinosinusitis refractory to other treatments with topical antibiotic therapy delivered by means of a large-particle nebulizer: results of a controlled trial. *Otolaryngol* 2001; **125**(3):265-9.
19. Barazi R, Bawab I, Dunia G, et al. The Use of Topical Intranasal Antibiotics in Pediatric Chronic Rhinosinusitis. *Ann Otolaryngol Rhinol* 2016; **3**(12):1150.
20. Mao T, Kim J, Peña-Hernández MA, et al; Yale SARS-CoV-2 Genomic Surveillance Initiative; Gopinath S, Wilen CB, Palm N, Dela Cruz CS, Iwasaki A. Intranasal neomycin evokes broad-spectrum antiviral immunity in the upper respiratory tract. *Proc Natl Acad Sci* 2024; **121**(18):e2319566121.