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# The theory of a "staphylococcus superantigen" in chronic rhinosinusitis with nasal polyps: myth or reality?

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**Abstract. – OBJECTIVE: The aim of our study was to search for evidence of a "staphylococcus superantigen" in chronic rhinosinusitis with nasal polyps.**

**PATIENTS AND METHODS: Sixty-nine patients with chronic rhinosinusitis with nasal polyps and 45 healthy controls were included in the study. All patients in the study and control groups underwent bacteriological and immunological examination on nasal smear samples. Total IgE and the following cytokines were tested in all patients: tumor necrosis factor (TNF), interleukin-1 (IL1), interleukin-6 (IL6), interleukin-8 (IL8).**

**RESULTS: The concentration of bacteria in the nasal cavity was much higher in patients in the study group compared to those in the control group, mainly due to staphylococci. In species identification of staphylococci, bacteria most represented were *S. aureus* and *S. epidermidis*. The greater the concentration of *S. aureus*, the lower the level of IgE. Proinflammatory cytokines were uniformly increased in patients with nasal polyps. The level of IgE was maximal in patients with chronic rhinosinusitis with nasal polyps with a poor growth of culture and minimal in patients with abundant growth, suggesting that in the latter the effect of eosinophilic inflammation on the disease was reduced, and conversely, the activity of eosinophilic inflammation was maximal with a poor seeding of the nasal cavity.**

**CONCLUSIONS: Although this study has some limits, our findings do not support the theory of a staphylococcus superantigen in which the IgE level and eosinophilic inflammation should increase with increasing activity of *Staphylococcus aureus*. Further research supported by a larger sample of patients is required to better delineate the role of a staphylococcus superantigen in the pathogenesis of patients with chronic rhinosinusitis with nasal polyps.**

Key Words
Chronic rhinosinusitis with nasal polyps, Staphylococci, *Staphylococcal superantigens*, *Staphylococcus aureus*, Antibiotics.

### List of Abbreviations

ESS: Endoscopic Sinus Surgery; CFU: colony-forming units; Me: median; TNF: tumor necrosis factor; IL1: interleukin-1; IL6: interleukin-6; IL8: interleukin-8.

## Introduction

Chronic rhinosinusitis with nasal polyps is a chronic disease of the nasal mucosa and paranasal sinuses; it has an inflammatory reaction on the level of pathogenesis, in which, depending on the form of inflammation, eosinophils or neutrophils may predominate[1-4]. Its prevalence in the population is quite high and may have a significant impact on quality of life[5]. In Skovde (Sweden), the prevalence of nasal polyps is 2.7% of the total population[6]. In Finland, it was determined that 4.3% of the adult population responded positively to the question of whether they ever had polyps in the nasal cavity[7]. In Denmark, polyps in the nasal cavity were found in 5 out of 19 autopsy cases[8]. In France, using a questionnaire specific to each disease, a 2.1% prevalence of nasal polyps was found in the general population[9]. Endoscopic Sinus Surgery (ESS) is widespread in treating chronic rhinosinusitis with nasal polyps and several studies have shown that it is an effective and safe treatment for patients with chronic rhinosinusitis with nasal polyps when drug therapy has



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failed[10-14]. Despite widespread occurrence, there is still no single point of view about the causes of nasal polyposis. Recently, some researchers adhered to the theory of a so-called "staphylococcus superantigen", which suggests that colonization by *S. aureus* leads to the formation of a superantigenic toxin that enhances local eosinophilic inflammation and the formation of polyps[15-24]. In support of this hypothesis, studies have shown a high correlation between the presence of staphylococci and polyps of the nose[15,16,25].

However, evidence for the role of a staphylococcus superantigen in the pathogenesis of nasal polyps is still insufficient. The aim of our study was to search for evidence of a staphylococcus superantigen *in* chronic rhinosinusitis with nasal polyps.

## Patients and Methods

### Patients

Sixty-nine patients with chronic rhinosinusitis with nasal polyps aged from 18 to 70 years of both sexes were included in the study. The control group included 45 healthy volunteers that matched the study group for sex and age. The study was performed in the Otolaryngology Department of our University Hospital; the study was specifically approved by the Ethical Committee of our University.

All patients in the study group entered the otolaryngology department for routine ESS treatment. Term of the disease in patients did not exceed 5 years; patients with earlier operations for polyposis were excluded from the study. All patients in the study and control groups underwent bacteriological and immunological examination on nasal smear (before surgery for patients in the study group). To determine the effect of bacterial concentration on the level of eosinophilic inflammation, patients with chronic rhinosinusitis with nasal polyps were divided into three groups depending on the growth of microorganisms: 14 patients with poor growth (20 colonies, 10x3 units of colony-forming units (CFU)/ml)); 28 patients (group 2) with moderate growth (21 to 100 colonies, 10x4 CFU/ml); 27 patients (group 3) with abundant growth (more than 100 colonies, from 10x4 CFU/ml). For a bacteriological study, a smear from the mucous membrane of the middle nasal passage was carried out, followed by sowing of microorganisms with the help of three nutrient differential diagnostic media. Total IgE and the following cytokines were tested in all patients: tumor necrosis factor (TNF), interleukin-1 (IL1), interleukin-6 (IL6), interleukin-8 (IL8).

### Statistical Analysis

Statistical processing of the results was carried out using the Statistica 7.0 application software package (StatSoft, Inc., 2004). The sample was processed by calculating the median (Me) and interquartile range in the form of 25th and 75th percentiles (C25 and C75). The reliability of the differences between the indices of independent samples was estimated from the nonparametric Mann-Whitney criterion, dependent samples using the Wilcoxon test. The critical level of significance ($p$) in testing the statistical hypotheses in this study was 0.05.

### Results

When studying the role of bacteria in patients with chronic rhinosinusitis with nasal polyps (study group), it was found that the total number of bacteria in these patients significantly exceeded the microbial landscape of the nasal cavity of subjects in the control group; 11,120,000 (6,051,004-516,650,004) CFU/ml *vs.* 10,000 (1,160-23,000) CFU/ml $p<0.001$). With the generic identification of bacteria, the concentration of staphylococci was dominant in both groups: 2,131,001 (1,600,000-4,520,002) CFU/ml in patients with chronic rhinosinusitis with nasal polyps and 10,000 (300-11,000) CFU/ml in healthy individuals. In species studies in healthy people, a higher titer showed *S. epidermidis* 1000 (100-1,000) CFU/ml, which corresponds to the norm. In patients with polyposis, most bacteria of the genus *Staphylococcus* were represented by *S. aureus* 500,000 (400,000-3,500,000) CFU/ml and *S. epidermidis* 500,000 (120,000-1,000,000) CFU/ml (Table I).

In spite of the fact that most bacteria were represented by staphylococci, in the species assessment of microorganisms in general, *St. pneumoniae* 10,000,000 (500,000-7,000,000) CFU/ml and *M. catarrhalis* 10,000,000 (500,000-25,000,000) CFU/ml were dominant in patients with chronic rhinosinusitis with nasal polyps.

When analyzing proinflammatory cytokines in patients in the study group, it was determined that all the cytokines tested were increased in comparison with subjects in the control group (Figure 1). This, undoubtedly, is associated with a pronounced inflammatory reaction to disease.

**Table I.** The main indices of dissemination of the nasal cavity in the study group (n = 69) and in the control group (n=45) (Me [C25- C75]).

| Microorganisms (CFU/ml) | Study group (n=69) | Control group (n=45) |
|---|---|---|
| Staphylococcus | 2,131,001 (1,600,000-4,520,002) | 10,000 (300-11,000) |
| S. aureus | 500,000 (400,000-3,500,000) | 100 (33-200)** |
| S. epidermidis | 500,000 (120,000-1,000,000) | 1,000 (100-1,000) |
| S. haemolyticus | 10,000 (10,000-100,000) | 100 (10-100)** |
| Streptococcus | 1,325,000 (500,000-8,500,000) | 1,000 (1,000-1,000)** |
| St. pneumonia | 1,000,000 (500,000-7,000,000) | 1,000 (1,000-1,000)** |
| Micrococcus | 5,000 (1,000-5,500) | 1,000 (550-1,000)* |
| Enterobacteriaceae | 10,000 (10,000-55,000) | 1,000 (55-10,000)** |
| M. catarrhalis | 1,000,000 (500,000-25,000,000) | 1,000 (1,000-1,000)** |

*$p$<0.01; **$p$<0.001.

It was also noted that IL8, at 45 (25-110) pg/mg, increased most intensively, against 5 (2-8) pg/mg in healthy individuals ($p$<0.01). IgE levels in patients in the study group were significantly higher than in the control group (Figure 2). The concentration in patients was 94 (17-165) IU/ml, against 7 (3-10) IU/ml in healthy subjects ($p$<0.001).

In patients with chronic rhinosinusitis with nasal polyps in the moderate- and abundant-growth groups, staphylococci also dominated, with values of 1,960,001 (1,465,051-2,321,001) CFU/ml and 4,730,002 (3,020,000-9,020,000) CFU/ml, respectively. However, unlike the groups as a whole, in patients with nasal polyps with abundant growth of microorganism, the highest concentration was in *S. aureus* - 3,500,000 (1,000,000-4,000,000) CFU/ml, both in species identification and among all microorganisms (Table II).

In the study of proinflammatory cytokines, there was no significant association with colony growth in patients with chronic rhinosinusitis with nasal polyps. In the study group, investigated cytokines (TNF, IL1, IL6, IL8) were uniformly increased in patients with nasal polyps. However, the level of IgE in the groups with different culture growth was different (Figure 3). It was maximal in patients with chronic rhinosinusitis with nasal polyps with a poor growth of culture - 150 (45-310) ME/mg - and minimal in patients with abundant growth - 34 (16-117) ME/mg ($p$<0.01). This suggests that in those patients where abundant growth of microorganisms is determined (due to the activity of *S. aureus*), the effect of eosinophilic inflammation on the disease was reduced, and conversely, the activity of eosinophilic inflammation was maximal with a poor seeding of the nasal cavity.

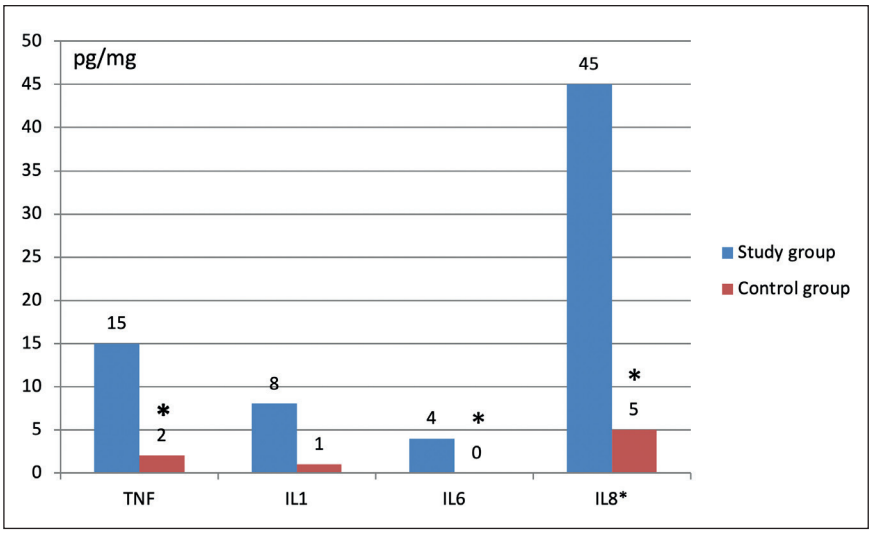


**Figure 1.** The level of proinflammatory cytokines (TNF, IL-1, IL-6, IL-8) in patients in the study group and in the control group (* - $p$<0.001).

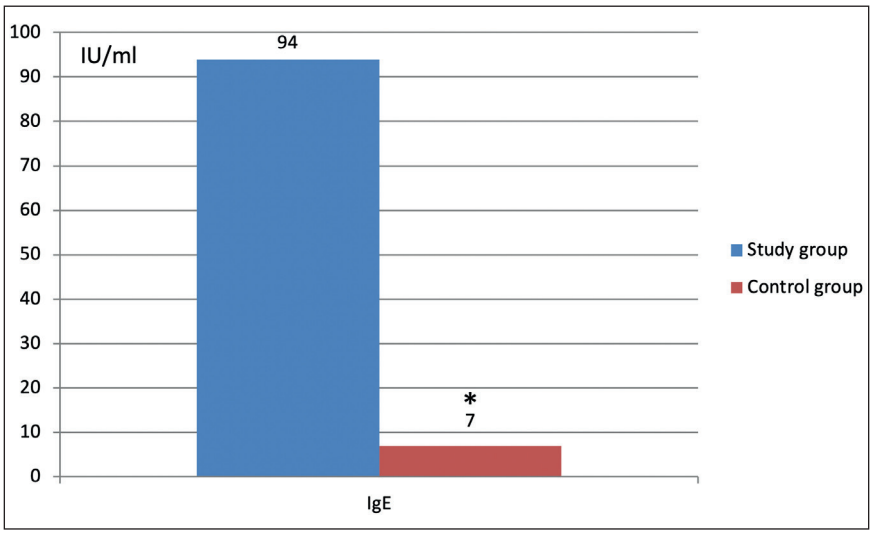


**Figure 2.** IgE concentration in patients in the study group and in the control group (* - $p<0.001$).

## Discussion

In the study of microflora in patients with chronic rhinosinusitis with nasal polyps, it was found that their growth was increased due to gram-positive microorganisms, mainly staphylococci. The greatest number of bacteria was represented by *St. pneumoniae* and *M. catarrhalis*, and in staphylococci - *S. aureus* and *S. epidermidis*. All the studied proinflammatory cytokines were increased, which indicates the presence of a pronounced inflammatory process in polyposis; this is in accordance with recent studies that focused on the role of proinflammatory cytokines in nasal polyposis[5,12-14,26-30]. In particular, IL8 has pronounced proinflammatory properties, causes

**Table II.** The main indices of dissemination of the nasal cavity in patients with chronic rhinosinusitis with nasal polyps (n = 69, Me (C25-C75). Patients were divided in three groups depending on the growth of microorganisms (poor growth, moderate growth, abundant growth).

| Microorganisms (CFU/ml) | Poor growth | Moderate growth | Abundant growth |
|---|---|---|---|
| *Staphylococcus* | 1,530,050 (1,510,000-1,631,000) | 1,960,001 (1,465,051-2,321,001) | 4,730,002 (3,020,002-9,020,002)* |
| *S. aureus* | 50,000 (10000-100000) | 450,000 (200,000-500,000) | 3,500,000 (1,000,000-4,000,000)** |
| *S. epidermidis* | 500,000 (10,000-1,000,000) | 400,000 (120,000-500,000) | 1,000,000 (500,000-3,750,000) |
| *S. haemolyticus* | 55,000 (10,000-100,000) | 10,000 (10,000-55,000) | 10,000 (10,000-110,000)* |
| *Streptococcus* | 575,000 (475,000-3,505,000) | 1,505,000 (500,000-22,500,000) | 1,500,000 (1,000,000-8,500,000 |
| *St. pneumonia* | 500,000 (500,000-5,000,000) | 1,000,000 (500,000-25,000,000) | 1,000,000 (500,000-7,000,000)** |
| *Micrococcus* | 7,750 (3,250-10,000) | 5,500 (1,000-5,500) | 1,000 (1,000-3,000) |
| *Enterobacteriaceae* | 32,500 (10,000-77,500) | 55,000 (10,000-100,000) | 10,000 (10,000-55,000) |
| *M. catarrhalis* | 1,250,000 (500,000-25,000,000) | 1,000,000 (500,000-25,000,000) | 1,000,000 (500,000-7,000,000)* |
| *Hem. influenzae* | 1,250,000 (500,000-25,000,000) | 750,000 (200,000-25,000,000) | 750,000 (500,000-7,000,000) |

*$p<0.01$; **$p<0.001$.

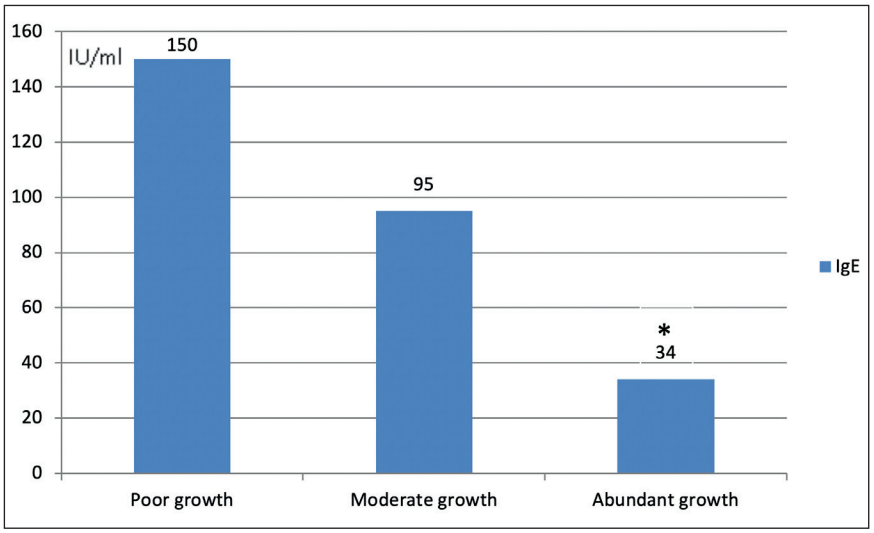


**Figure 3.** The ratio of IgE concentration and microbial flora level in patients with chronic polyposis rhinosinusitis (study group, n = 69, Me (C25-C75), * - $p<0.01$).

the expression of intercellular adhesion molecules, and enhances the adhesion of neutrophils to endothelial cells and subendothelial matrix proteins. The pronounced increase of IL8 in patients with nasal polyps is indicative of the role of neutrophilic inflammation in the disease [31-33]. IgE levels in patients with chronic rhinosinusitis with nasal polyps were significantly higher than in healthy people. It is known that the activity of this immunoglobulin is due to eosinophilic inflammation, which plays an important role in chronic rhinosinusitis with nasal polyps [27,34-37].

Much debate exists on the role of staphylococcus aureus superantigens in chronic rhinosinusitis. A recent meta-analysis on 12 studies including 340 cases and 178 controls that indicated that the staphylococcus aureus superantigens may be a risk factor for chronic rhinosinusitis with nasal polyps, and the presence of the staphylococcus aureus superantigen may be related to the disease severity of the disease [38]. In our study, when patients were divided into three groups depending on the degree of dissemination, it was determined that the staphylococcus was also dominant, with a predominance of *S. aureus* in the moderate- and abundant-growth groups. This suggests that in the group with pronounced culture growth in patients with chronic rhinosinusitis with nasal polyps, *S. aureus* plays the greatest role. Moreover, the inverse dependence of the IgE level on the level of dissemination of the mucous membrane of the nasal cavity was determined.

The main limitation of the present study is the small sample size that may have affected the statistical power of our analysis.

## Conclusions

Our results show that the higher the titer of nasal cavity colonization, the lower the activity of eosinophilic inflammation. These findings, that may be affected by the small sample size of the study group, do not confirm the theory of a staphylococcus superantigen in which eosinophilic inflammation should increase with the activity of *Staphylococcus aureus*. Further research supported by a larger sample of patients is required to better delineate the role of a staphylococcus superantigen in the pathogenesis of patients with chronic rhinosinusitis with nasal polyps.

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### Conflict of Interests

The authors declare that they have no conflict of interest.

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